

Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases

Eleftherios Pelechas
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“To our patients who not only trusted their health but also allowed us to take photos of their clinical manifestations in order to teach students and other health professionals”

“To all the medical, nursing and supporting staff who worked in the rheumatology clinic all these years and gave battles against pain, giving hope, courage and strength to our patients”

Preface

This first edition of the *Illustrated Handbook of Rheumatic and Musculoskeletal Diseases* offers a practical guide to all those who deal with patients suffering from rheumatic conditions and related disorders. Nowadays, rheumatic conditions are common both in general and hospital practice and are a major source of morbidity and mortality. Skin and musculoskeletal manifestations may be the first signs of a rheumatic disease, so it is of imperative significance to perform a thorough clinical examination of these systems. The philosophy of this manuscript relies on less text and more figures in order to make the reader confident to recognise different presentations of the same disease. To further reinforce this philosophy, apart from the representative photos presenting clinical manifestations, imaging findings from different imaging modalities as well as histopathologic features have been added. Nevertheless, it is no way intended to be exhaustive. Having the privilege to attend the rheumatology clinic since 1981 taking care of a large number of patients, I always had the passion of collecting difficult and educational clinical cases in order to use them for educational purposes. Over the years, an enormous archive of clinical, imaging and histological pictures has been created. Doctor E. Pelechas, a young, enthusiastic rheumatologist, captured the idea of putting this material in order, so as to create an illustrated book. This idea was welcomed and supported by Professor P.V. Voulgari and the attending rheumatologist E. Kaltsonoudis. Our aim is to become a valuable guide and educator not only for rheumatologists in training and practice but also for general practitioners, orthopaedics, dermatologists, medical students and other medical specialists.

Every chapter is divided into three parts. The first part starts with a general description of the disease including introduction, epidemiology, signs and symptoms, diagnostic modalities and management. The second part includes figures with a short explanation. Where needed, more than one figure of the same ailment are presented in such a manner that can be more understandable by the reader. The third part includes the references and suggestions for further reading.

It is our hope that both doctors from different specialties and their patients will take great benefit from this book.

Ioannina, Greece

Alexandros A. Drosos

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Abbreviations

AAV	ANCA-associated vasculitis
ACE	angiotensin-converting enzyme
ACL	anterior cruciate ligament
aCL	anticardiolipin
ACPA	anti-citrullinated peptide antibodies
ACR	American College of Rheumatology
ADR	adverse drug reactions
AIHA	autoimmune haemolytic anaemia
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANCA	antineutrophil cytoplasmic antibodies
anti-CCP	anti-cyclic citrullinated peptide
AOOSD	adult-onset Still's disease
aPL	antiphospholipid
aPTT	activated partial thromboplastin time
ARD	autoimmune rheumatic disease
AS	ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASS	antisyntetase syndrome
AxSpA	axial spondyloarthritis
AZA	azathioprine
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCP	basic calcium phosphate
bdMARDs	biologic disease-modifying antirheumatic drugs
BMI	body mass index
cANCA	cytoplasmic antineutrophil cytoplasmic antibodies
CASPAR	Classification Criteria for Psoriatic Arthritis
CCLE	chronic cutaneous lupus erythematosus
CD	colour Doppler
CHB	congenital heart block
CL	cutaneous lupus

CLE	cutaneous lupus erythematosus
CMC	carpometacarpal joint
COPD	chronic obstructive pulmonary disease
CP	cyclophosphamide
CPFE	combined pulmonary fibrosis and emphysema
CPPD	calcium pyrophosphate dihydrate disease
CR	conventional radiography
CRP	c-reactive protein
Cryo	cryoglobulin
CS	corticosteroids
CSA	cyclosporine
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
CT	computed tomography
CTD	connective tissue disease
CTLA-4	cytotoxic T-lymphocyte antigen 4
CTS	carpal tunnel syndrome
CXR	chest X-ray
DECT	dual-energy computed tomography
DEXA	dual-energy X-ray absorptiometry scan
DIP	distal interphalangeal joint
DISH	diffuse idiopathic skeletal hyperostosis
DLE	discoid lupus erythematosus
DM	dermatomyositis
DMARDs	disease-modifying antirheumatic drugs
dRVVT	dilute Russell's viper venom time
ds-DNA	double-stranded DNA
DSM	dermatomyositis sine myositis
EF	eosinophilic fasciitis
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
ELP	electrophoresis
EMG	electromyography
EN	erythema nodosum
ENA	extractable nuclear antigens
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FBC	full blood count
GA	granuloma annulare
GCA	giant-cell arteritis
GPA	granulomatosis with polyangiitis
H&E	hematoxylin & eosin
HADD	hydroxyapatite crystal deposition disease
HAP	hemiarthroplasty
HC	hyaline cartilage
HCQ	hydroxychloroquine

HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HMGR	3-hydroxy-3-methylglutaryl-CoA reductase
HPV	human papillomavirus
HRCT	high-resolution computed tomography
HS	hidradenitis suppurativa
HSP	Henoch-Schönlein purpura
HZ	herpes zoster
IBM	inclusion-body myositis
IC	immune complex
ICU	intensive care unit
IF	immunofluorescence
IFN	interferon
Ig	immunoglobulin
IgG4-RD	immunoglobulin G4-related disease
IL-	interleukin
IP	Interphalangeal
IVIG	intravenous immunoglobulin
KCS	keratoconjunctivitis sicca
LA	lupus anticoagulant
LD	Lyme disease
LDI	Leeds dactylitis instrument
LE	lupus erythematosus cell
LEF	leflunomide
LET	lupus erythematosus tumidus
LFT	liver function tests
MALT	mucosa-associated lymphoid tissue
MCP	metacarpophalangeal
MCTD	mixed connective tissue disease
mDIXON	modified Dixon
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MRI	magnetic resonance imaging
mRSS	modified Rodnan skin score
MSA	myositis specific autoantibody
MSK	musculoskeletal
MST	modified Schober's test
MSU	monosodium urate
MSUS	musculoskeletal ultrasound
MTP	metatarsophalangeal
MTX	methotrexate
NAM	necrotising autoimmune myositis
NOF	neck of femur

NSAIDs	non-steroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NSF	nephrogenic systemic fibrosis
NSIP	non-specific interstitial pneumonitis
NVC	nailfold videocapillaroscopy
OA	osteoarthritis
OCD	osteochondritis dissecans
OCI	osteitis condensans ilii
ON	osteonecrosis
PA	posteroanterior view
PAD	peptidylarginine deiminase
PAH	pulmonary arterial hypertension
PAN	polyarteritis nodosa
pANCA	perinuclear antineutrophil cytoplasmic antibodies
PASI	psoriasis area and severity index
PCL	posterior cruciate ligament
PD	proton density
PDS	power Doppler sonography
PET	positron emission tomography
PIP	proximal interphalangeal joint
PM	polymyositis
PMN	polymorphonuclear
PR3	proteinase 3
PsA	psoriatic arthritis
PTPN22	protein tyrosine phosphatase non-receptor type 22
PUK	peripheral ulcerative keratitis
RA	rheumatoid arthritis
RANKL	receptor activator of nuclear factor kappa-B ligand
RF	rheumatoid factor
RN	rheumatoid nodule
RNP	ribonucleoprotein
ROM	range of motion
RP	Raynaud's phenomenon
RS3PE	remitting seronegative symmetrical synovitis with pitting oedema syndrome
RTX	rituximab
RV	rheumatoid vasculitis
SAPHO	synovitis, acne, pustulosis, hyperostosis and osteitis syndrome
SCCJ	sternocostoclavicular joint
SCL	scleroderma
SCLE	subacute cutaneous lupus erythematosus
SD	standard deviation
SE	shared epitope
SF	synovial fluid
SI	sacroiliac

SLE	systemic lupus erythematosus
SLS	shrinking lung syndrome
Sm	Smith antibodies
SpA	spondyloarthropathies
SPE	serum protein electrophoresis
SRP	signal recognition particle
SS	Sjögren's syndrome
SSZ	sulphasalazine
ST	Schober's test
TA	Takayasu's arteritis
THA	total hip arthroplasty
THR	total hip replacement
TKR	total knee replacement
TM	transverse myelitis
TNF-i	tumour necrosis factor inhibitor
tsDMARDs	targeted synthetic disease-modifying antirheumatic drugs
UIP	usual interstitial pneumonia
ULN	upper limit of normal
UV	ultraviolet
WG	Wegener's granulomatosis
WHO	World Health Organization
β2-GPI	beta2-glycoprotein I

Chapter 1

Examination of the Musculoskeletal System



1.1 Introduction

Rheumatology deals with autoimmune diseases that in great part affect the joints. Thus, the examination of the musculoskeletal system is of great importance. All joints can be affected, so a thorough and minute examination should be carried out for each patient. The joints of the limbs and spine should be assessed for their function. Measurement of joint range of motion (ROM) and assessment of muscle strength are essential parts of the examination. There is no standard technique for the examination of the joints, but a common sequence must be followed in order to avoid missing any clinical information from the examination. Inspection, palpation, joint ROM, muscle strength and also conduction of special tests/provocative maneuvers if needed, is a proposed sequence. The clinician should be focused on the symptomatic area but must be aware that sometimes the referring pain from the patient to a specific area may radiate from a distant point. For this reason, it is proposed to examine also the joints that lie proximal and distal to the apparently affected.

Some questions that can be addressed to the patient before the examination are the following:

- Is there a functional limitation of the joint/joints affected?
- Symptoms involve one or more joints?
- Are the symptoms acute or slowly progressive?
- If the patient mentions that he/she had an injury, try to find out the mechanism.
- Did you have any prior problems with this/these joint/s?
- Are there any systemic symptoms?

After asking the above-mentioned questions make sure that the affected area is well-exposed for examination. Never examine a joint above the patient's clothes. Then, start a minute examination.

1.2 Clinical Examination

Start the examination by assessing patient's gait and try to figure out if there is any obvious pain or deformity while walking.

Inspection: look for signs of inflammation (swelling, redness), any obvious injury and deformities. Always compare the contralateral joint.

Palpation: is the affected joint warm (inflammation)? Feel for any points of tenderness. Do not forget to examine the surrounding structures (e.g. many patients complain about knee pain but in fact pain comes from pes anserinus pathology).

Range of Motion (ROM): check for active and passive movements of the affected joint. Feel for clicks, crepitus or any related abnormal finding.

Muscle strength and neuromuscular assessment.

Special tests/provocative maneuvers: some examples that are frequently used in the everyday practice are the Tinel's and Phalen's test (carpal tunnel syndrome),

McMurray's test (meniscal damage), Gaenslen test (assessment of the sacroiliac joint), Finkelstein's test (de Quervain's tenosynovitis) and more.

As a general rule that can help both the patient and the clinician is the examination of the unaffected side first (in cases of severe pain). This helps patients to gain confidence and physicians to assess the normal ROM of the contralateral side.

1.3 Imaging Modalities

In modern rheumatology various modalities of joint imaging are used. Conventional radiography, computed tomography, magnetic resonance imaging, bone scintigraphy, positron emission tomography, musculoskeletal ultrasonography, and bone densitography are the modalities used in order to assess bone lesions, ligaments, joints and soft-tissue changes.

Conventional radiography (CR): this imaging modality was once the standard method for assessing the presence of a disease. Also, serial films can be used to assess change or response to treatment. Bone erosions, subchondral cysts, joint space narrowing, subluxations, malalignment, ankylosis, periarticular osteopenia, bone sclerosis, bony proliferations, calcifications, and soft-tissue swelling are some of the findings in various rheumatic diseases. The disadvantage of this modality is the early bone changes that are not seen in plain x-rays.

Computed tomography (CT): it can be used for the detection of calcified tissues that are less well visualized with magnetic resonance imaging (MRI). High resolution CT (HRCT) increases the accuracy of CT imaging in sacroiliitis but nowadays, MRI is more accurate. Dual-energy CT (DECT) imaging helps in computerized quantification of tophus volume in peripheral joints.

Magnetic resonance imaging (MRI): sacroiliitis, enthesitis and temporomandibular joints may be better seen in MRI. Subchondral oedema may be seen in the posteroinferior part of the sacroiliac joint in very early stages of sacroiliitis, therefore it is the investigation of choice in early spondyloarthropathies (SpA). It is also highly sensitive to detect bone erosions in the hands and wrists of rheumatoid arthritis (RA) patients. This imaging modality is safe even during pregnancy as it does not use ionizing radiations and it is highly sensitive for the detection of early inflammation.

Scintigraphy: nowadays, bone scintigraphy is not a widely used technique since its diagnostic accuracy is low for the detection of inflammation.

Musculoskeletal ultrasound (MSUS): it is a safe to use imaging technique and it is helpful in diagnosing Baker's cyst, detection of fluid collections in joints, bursae, tendon sheaths and soft tissues, synovial thickening, and bone erosions. With the use of Power Doppler inflammatory foci are easily detected. The major disadvantage of this imaging modality is that it is an operator-dependent technique.

Positron emission tomography (PET) scan: assesses the metabolic activity of synovitis.

Dual-energy x-ray absorptiometry scan (DEXA): is used for the assessment of osteoporosis (hip and spine). In patients >65 years old, hip DEXA is preferred as osteophytes and vascular calcification interferes with bone mineral density measurement in spine.

1.4 Gait



Fig. 1.1 Gait

Figure 1.1a Anterior assessment.

Figure 1.1b Posterior assessment.

Figure 1.1c Standing on heels test for assessment of the S1 nerve.

Figure 1.1d Standing on toes test for assessment of the L4/L5 nerves.

Ask the patient to walk in the examination room, turn and walk back. Observe for any asymmetry present as well as the ability to turn quickly. By doing so, you are able to observe for any asymmetry of the shoulders, malalignment of the spine, antalgic gait, joint swellings, muscle atrophy and ROM of multiple joints. Finally, any foot pathology (pes planus, pes cavus, hallux valgus) can be easily observed.

1.5 Examination of the Shoulder



Fig. 1.2 Shoulder

Figure 1.2a Flexion.

Figure 1.2b, c Elevation.

Figure 1.2d Abduction.

Figure 1.2e Abduction and partial external rotation.

The shoulder joint or glenohumeral joint is a synovial ball and socket joint and has three bony structures: scapula, humerus and clavicle which are held together by ligaments and an intricate web of muscles. Expose both shoulders and compare both sides for any swellings, discoloration, deformities or muscle atrophy. Look for any asymmetry or shoulder impingement. Always remember that shoulder pain may be referred by other regions such as neck and abdomen, so a good personal history should be obtained. Patients should be able to move their hands to position over head (0–180° – flexion, elevation). Assess also for abduction movements (normal range 0–180°).



Fig. 1.3 Shoulder

Figure 1.3a External rotation.

Figure 1.3b Internal rotation.

Figure 1.3c Abduction and external rotation.

Figure 1.3d Adduction, extension and internal rotation.

Check for any limitation of ROM during external and internal rotation of the shoulders. Ask the patients to put their hands behind their head and then behind their back. Assess shoulder abduction and external rotation and shoulder adduction, extension and internal rotation respectively. Usually, these are the first movements to be affected when there are shoulder problems. A good knowledge of the anatomy of the shoulder is very helpful in order to understand different pathologies that may arise. Supraspinatus is not only an initiator of abduction, but acts throughout the range of abduction of the shoulder. Infraspinatus and teres minor muscles lie below the scapular spine and are external rotators of the shoulder. Infraspinatus primarily acts with the arm in neutral and teres minor is more active with external rotation in 90° of abduction. Subscapularis is the main internal rotator of the shoulder. It is the largest and strongest cuff muscle.

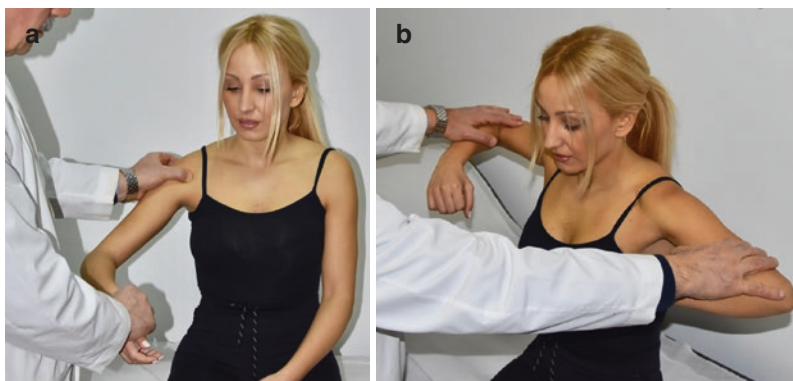


Fig. 1.4 Shoulder

Figure 1.4a Palpation.

Figure 1.4b Resisted abduction (proximal muscles).

Palpate the joint of shoulder finding anatomic landmarks that can help you out in distinguishing different anatomic structures that can produce pain (i.e. palpation of the sub-acromial space may produce pain if tendons/bursa inflamed – Fig. 1.4a, index finger of the examiner). Also, palpate biceps tendon in the bicipital groove, if pain appears then it may be a sign of tendinitis – Fig. 1.4a, thumb of the examiner). Resisted tests can assess the muscle strength, as in Fig. 1.4b. Proximal muscles are usually affected in various myopathies.

1.6 Examination of the Elbow

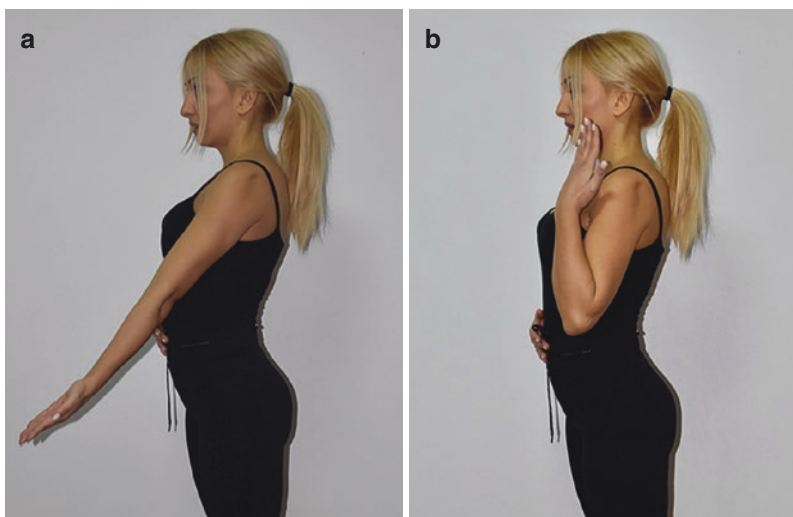


Fig. 1.5 Elbow

Figure 1.5a Extension.

Figure 1.5b Flexion.

Figure 1.5c Pronation.

Figure 1.5d Supination.

The elbow is a synovial hinge joint. The three bones of the elbow (humerus, radius, ulna) are surrounded by a common joint capsule. Flexion and extension are the two main movements of the joint. Pronation and supination movements occur at the radioulnar joints. When bony erosions develop then the ROM of the elbow is affected. Passively flex and extend the elbow and look for hyperextension or limited ROM.

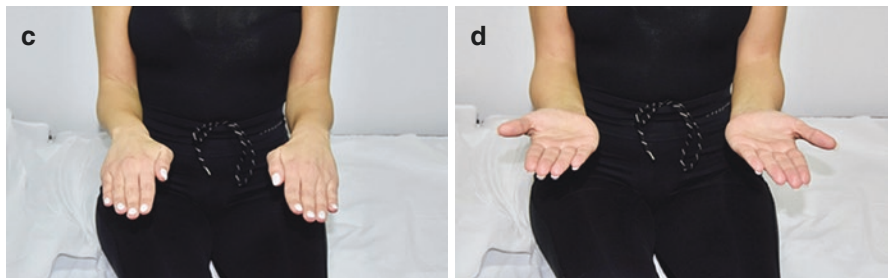


Fig. 1.5 (continued)

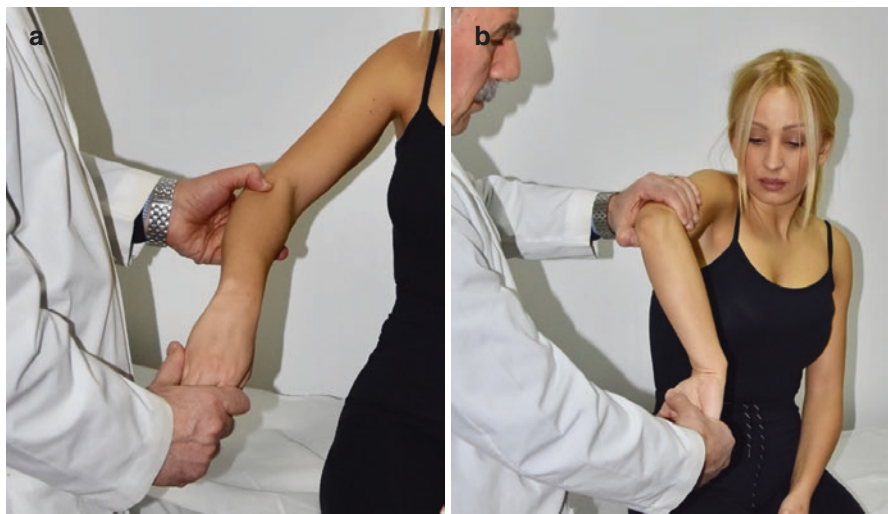


Fig. 1.6 Elbow

Figure 1.6a Lateral epicondyle palpation.

Figure 1.6b Medial epicondyle palpation.

Figure 1.6c Resisted extension.

Figure 1.6d Resisted flexion.

Palpate the elbow for any deformities or tender points (lateral/medial epicondylitis). The olecranon is a common site for bursitis and rheumatoid nodules. Check the muscle strength.

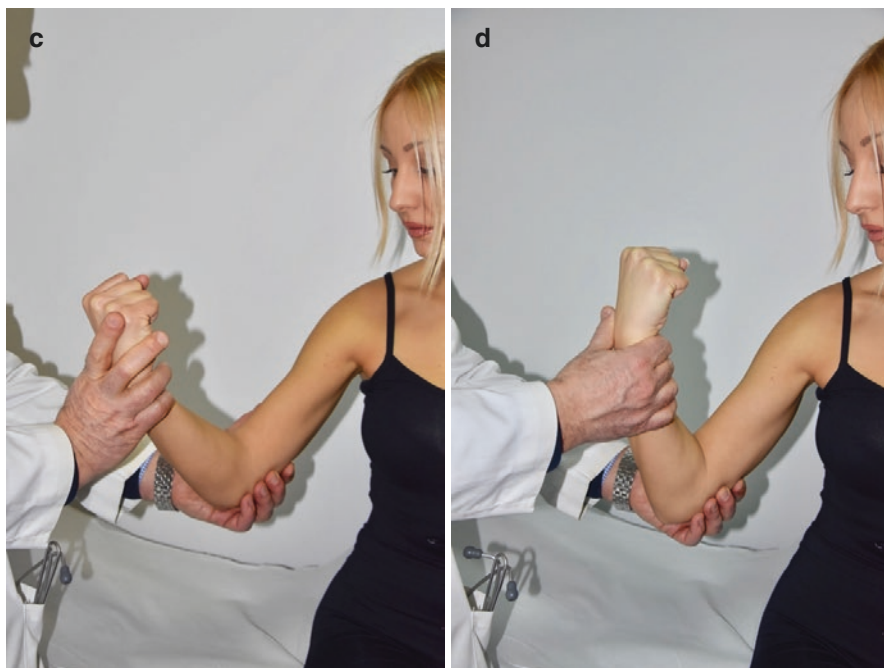


Fig. 1.6 (continued)

1.7 Examination of the Wrist

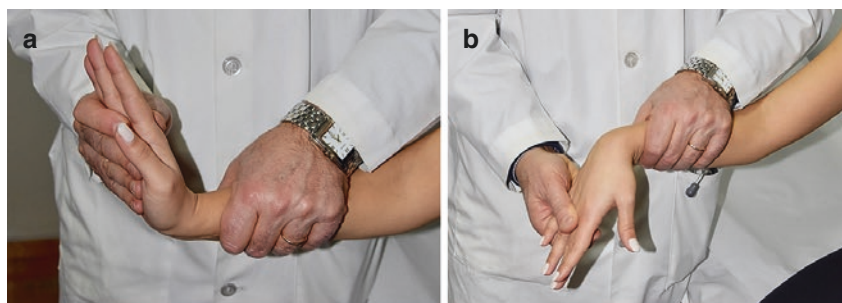


Fig. 1.7 Wrist

Figure 1.7a Extension.

Figure 1.7b Flexion.

Figure 1.7c Resisted extension.

Figure 1.7d Resisted flexion.

Figure 1.7e Palpation.

Look for any deformities. Check with active and passive movements the ROM of the wrist. Extension, flexion, and lateral movements (radial and ulnar) must be free of pain. In RA, limited ROM is common. Palpate over the wrist for tenderness or synovial swelling. Trauma is another frequent cause of wrist pain. Complications after trauma e.g. scaphoid fracture, may include avascular necrosis or post-traumatic arthritis.

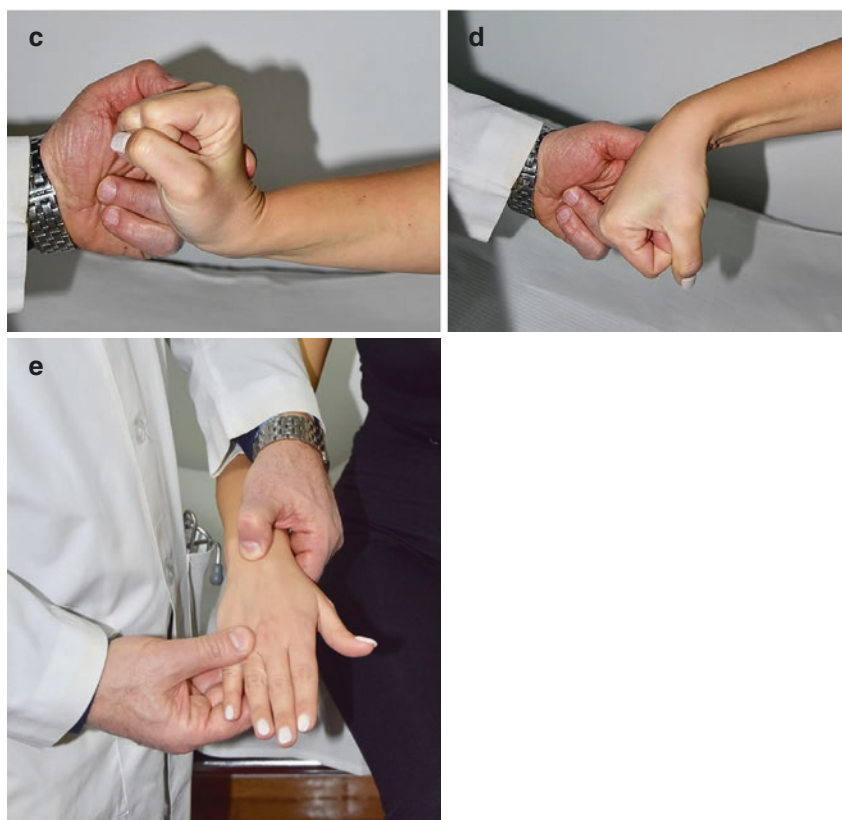


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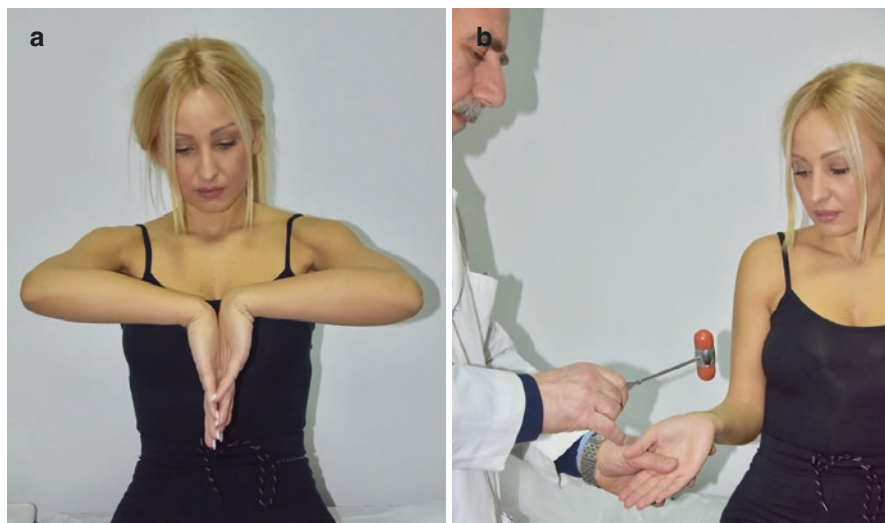


Fig. 1.8 Wrist

Figure 1.8a Phalen's test.

Figure 1.8b Tinel's test.

Phalen's and Tinel's tests are used to assess the wrist for carpal tunnel syndrome (CTS). CTS is the most commonly reported nerve compression syndrome. First, ask the patient to push the dorsal surface of his/her hands together into a maximum flexion and hold this position for 30–60 s (Fig. 1.8a). This position will compress the median nerve between the transverse carpal ligament and the anterior border of the distal end of the radius. Then, percuss the median nerve at carpal tunnel in wrist either by using the middle finger or a reflex hammer (Fig. 1.8b). The test is positive when pain and/or tingling is reproduced along the course of the median nerve. Durkan's test is another maneuver that can be used in order to diagnose CTS. It is a variation of Tinel's test. The examiner presses thumbs over carpal tunnel and holds pressure for approximately 30 s. The test is positive when pain or paraesthesia in the median nerve distribution develops.

Even if the above-mentioned tests have a high sensitivity and specificity for CTS pathology, nerve conduction studies are the “gold standard” diagnostic tool for the assessment of neuropathies such as CTS. MRI in CTS has low sensitivity and specificity but, on the other hand, MSUS is useful in examining CTS. Enlargement of the nerve seems to be the most sensitive and specific criterion.

1.8 Examination of the Hand



Fig. 1.9 Hand

Figure 1.9a Active make a fist in order to assess flexion of fingers.

Figure 1.9b Resisted finger abduction.

Figure 1.9c Palpation of the 1st carpometacarpal (CMC) joint.

Figure 1.9d Palpation of proximal interphalangeal (PIP) joints.

Figure 1.9e Squeeze across the metacarpophalangeal (MCP) joints.

Look for any swelling or deformities. Bouchard's and Heberden's nodules are common findings especially in women over the age of 65. Swan-neck and boutonniere deformities are common findings in RA. Palpate over each joint of the hand (MCP's, PIP's, DIP's – distal interphalangeal joints). Squeezing across the MCP's can be used for the assessment of pain.

1.9 Examination of the Spine – Cervical Spine

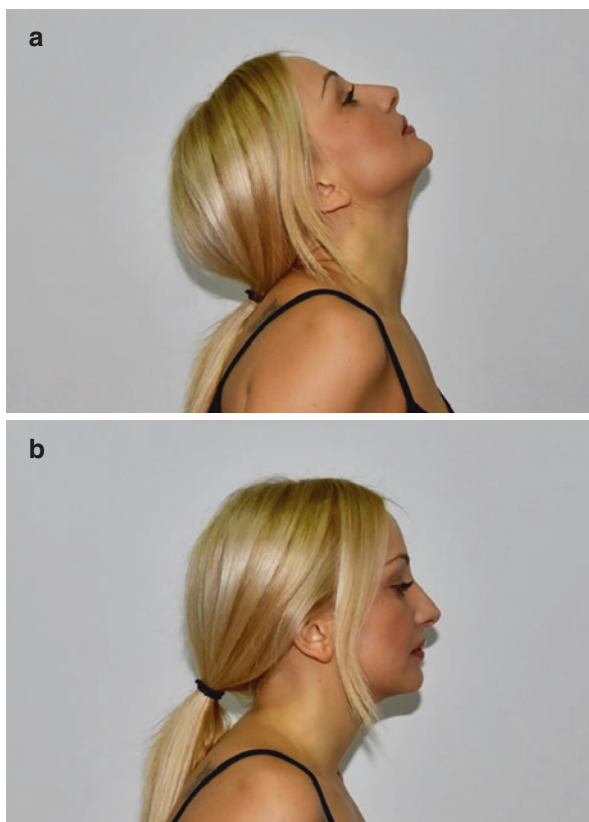


Fig. 1.10 Cervical spine

Figure 1.10a Hyperextension.

Figure 1.10b Extension.

Figure 1.10c Flexion.

Pain and stiffness of the cervical spine is not uncommon for both males and females and is a common problem not only for the rheumatic patients.

Postural neck pain is very common especially in those who have sedentary jobs. Acute neck pain may appear after a sudden movement of the neck accompanied by striking protective muscle spasm and limitation of cervical movements. Degenerative changes are the most common finding in patients after the fifth decade of life. RA frequently involves the neck. Progressive subluxation of the cervical spine, particularly at the atlanto-axial and mid-cervical levels may appear. Ankylosing spondylitis (AS) limits the ROM of the cervical spine. Cervical spondylosis or cervical spine osteoarthritis (OA) is a very common condition that usually affects older patients and it occurs due to the normal wear-and-tear of aging.

Ask patient to actively flex and extend the neck to assess the ROM. Ask for headaches or any neurologic symptoms that can be attributed to the cervical spine. For example, when a nerve root in the cervical spine becomes compressed or irritated by a problem in the neck, symptoms can appear anywhere from the shoulder all the way down into the arm, hand and fingers. Cervical myelopathy is another condition and it refers to compression on the cervical spinal cord.

Fig. 1.10 (continued)**Fig. 1.11** Cervical spine

Figure 1.11a Right rotation.

Figure 1.11b Left rotation.

Figure 1.11c Right lateral flexion.

Figure 1.11d Left lateral flexion

Ask patient to look over the shoulder or look back to assess the ROM during rotation of the neck. Look if the movement is equal on either side. Normal cervical ROM for rotation is 90° of rotation to both sides and for lateral flexion approximately $20\text{--}45^\circ$ on both sides.

In AS most cervical ROMs decline during disease duration, playing a marked role in functional impairment. In some patients with complete fusion of the cervical spine the ROM may be lost completely.

Degenerative changes of the cervical spine may also produce impairment of the ROM or pain during the examination to all directions. Different imaging modalities may help to assess in cases of restricted motions.

1.10 Examination of the Spine – Thoracic Spine

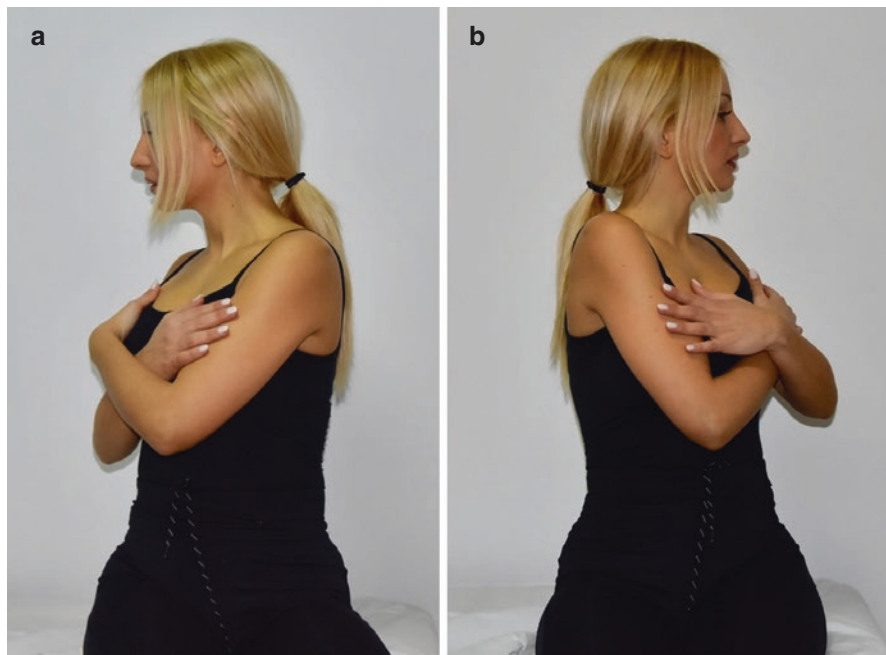


Fig. 1.12 Thoracic spine

Figure 1.12a Right rotation.

Figure 1.12b Left rotation.

Thoracic spine has a restricted ROM in comparison with the cervical and lumbar spine. Flexion, extension, lateral flexion, and left/right rotation are the movements that can be done by the thoracic spine. Ask the patient to stand, and look at the spine from the side. Try to make an assessment of the thoracic curvature, noting whether the curve is regular and if apparently increased. If the curvature is increased, especially in the elderly, senile kyphosis may be the cause. The same pattern can be seen in patients suffering from AS. If there is an angular kyphosis, with a gibbus or prominent vertebral spine, the commonest cause is fracture (trauma, osteoporosis). Finally, ask the patient for a deep inspiration and assess if the rib cage is moving appropriately. In AS patients you can even measure the rib cage expansion. Diffuse idiopathic skeletal hyperostosis (DISH) may produce diffuse pain along the spine and especially the thoracic spine. Conventional radiography may help to diagnose this disorder. Check also for scoliosis and palpate along the vertebrae for tender points.

1.11 Examination of the Spine – Lumbar Spine



Fig. 1.13 Lumbar spine

Figure 1.13a Flexion.

Figure 1.13b Extension.

Figure 1.13c Right lateral flexion.

Figure 1.13d Left lateral flexion.

Back pain is one of the commonest complaints which may cause significant disability. Look and palpate for any abnormal findings. Special tests can be done to assess pain and decreased ROM.

1.12 Examination of the Hip & Pelvis

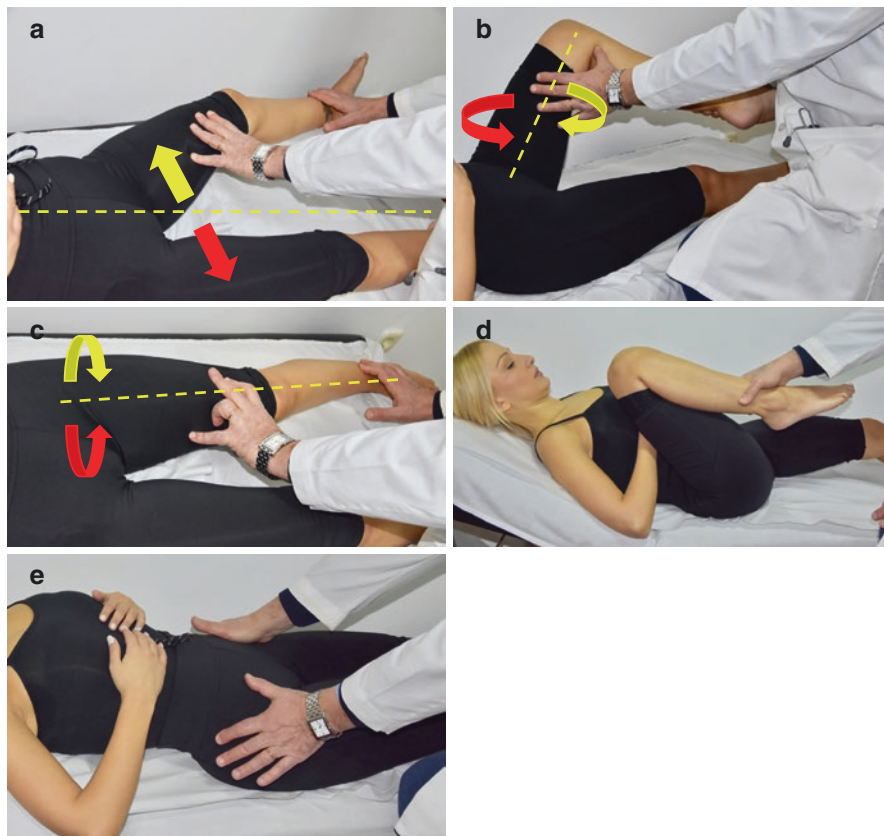


Fig. 1.14 Hip and pelvis

Figure 1.14a Left hip abduction – away from the middle line (yellow arrow). Left hip adduction – towards the middle line (red arrow).

Figure 1.14b Left hip external rotation (yellow curved arrow) and internal rotation (red curved arrow).

Figure 1.14c Log roll of the left hip – internal rotation (yellow curved arrow) and external rotation (red curved arrow).

Figure 1.14d Hip flexion.

Figure 1.14e Squish test for the assessment of the sacroiliac joints.

The pelvis and hips are frequently involved in OA. The sacroiliac joints are involved in the sero-negative SpA. There are various tests for the assessment of the sacroiliac joints and the hips. Pain is often poorly localised in the hip, groin, buttock or trochanter, and may be referred to the knee. Thus, the clinician should always make an assessment of the hips. The hip joints are frequently involved in various inflammatory arthritides as well as in OA.

1.13 Examination of the Knee

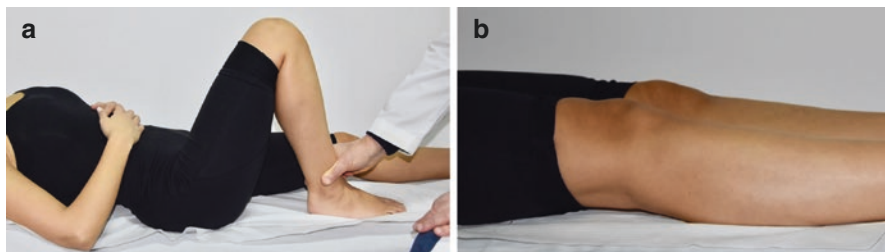


Fig. 1.15 Knee

Figure 1.15a Flexion.

Figure 1.15b Extension.

Flexion and extension are the major movements of the knees. Feel for crepitus of the knees. In restricted flexion check for Baker's cyst. MSUS may be helpful in this direction.

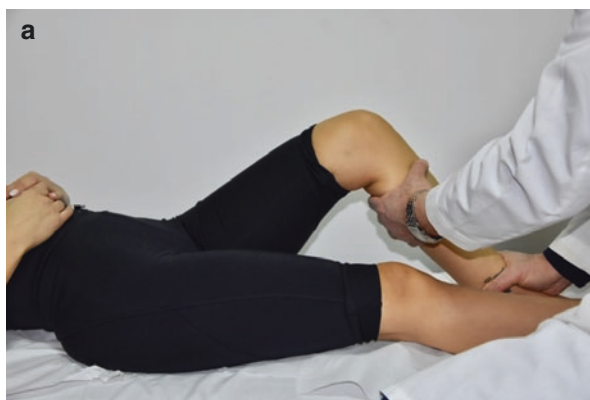


Fig. 1.16 Knee. Assessment of the ligaments

Figure 1.16a Anterior drawer test. Lower leg pulled up to check knee joint laxity (anterior cruciate ligament).

Figure 1.16b Posterior drawer test. Lower leg pushed down to check knee joint laxity (posterior cruciate ligament).

Figure 1.16c Knee varus stress test for the assessment of the lateral collateral ligament. The examiner applies outward pressure at medial thigh with one hand and inward pressure from lateral ankle with the other hand (red arrows). The knee valgus stress test is used for the assessment of the medial collateral ligament. The examiner applies inward pressure at lateral thigh with one hand and outward pressure from medial ankle with the other hand (yellow arrows). The maneuver should be done firstly with the knee in extension and in 30° flexion.

The cruciate ligaments are prone to trauma. There is a general association between anterior cruciate ligament (ACL) degeneration and aging and between ACL degeneration and cartilage degeneration. ACL changes may precede or initiate cartilage damage or occur simultaneously with or subsequent to cartilage lesions. The posterior cruciate ligament (PCL) is injured less frequently than other knee ligaments.

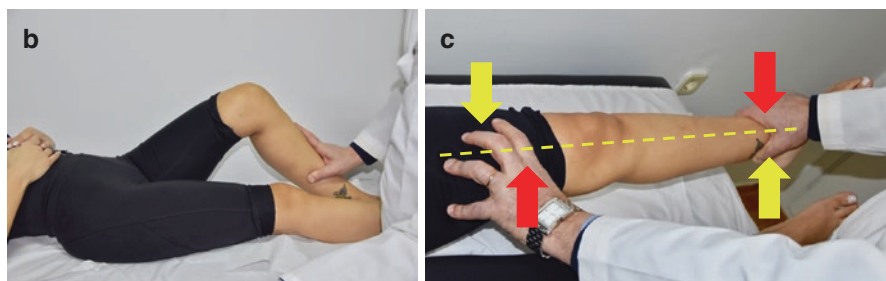


Fig. 1.16 (continued)

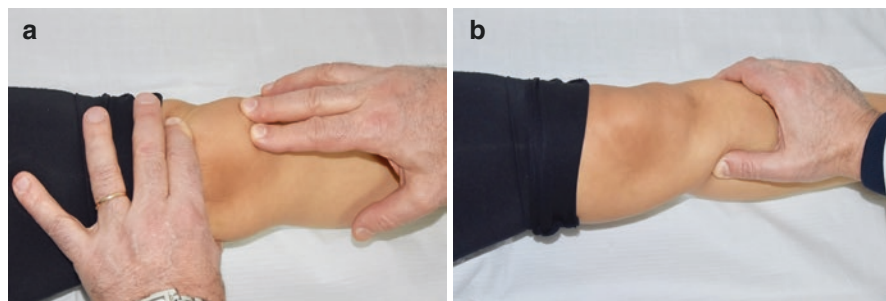


Fig. 1.17 Knee

Figure 1.17a Palpation of the patella.

Figure 1.17b Assessment for pes anserinus.

Figure 1.17c, d Patellar tendon reflex.

Inspect the knees for swelling, lumps, discoloration, scars of previous injury or surgery, and feel the temperature. Always compare the contralateral knee. Palpate for effusions, feel the temperature on both knees. OA commonly affects the knees especially in obese patients and women over the age of 65 years old. In OA, the articular cartilage undergoes progressive change, flaking off into the joint and thereby producing the narrowing that is a striking feature of radiographs of this condition. In RA the knee is characteristically warm to the touch, there is effusion, limitation of movements, tenderness and pain. The seronegative SpA may also develop the same clinical picture. Crystal arthropathies may also involve the knee. The clinical picture may be severe with the patient being unable to bend or even weight bear. In such cases, knee joint aspiration is required in order to exclude septic arthritis which constitutes a rheumatological emergency. A prompt diagnosis and treatment due to its rapid destructive nature must be carried out.

Check for malalignment of the knee joints. Genu varum may be seen in patients with advanced OA. Genu valgum is seen most often in association with RA.

CR, MSUS and MRI techniques can be used in order to elucidate cases that cannot rely only on the clinical examination. Pes anserinus is frequently the cause of knee pain. It is a gradually worsening pain on the medial knee and below the patella, at the insertion of three tendons (gracilis, sartorius, semitendinosus). The clinical examination of the knee can be followed by the patellar tendon reflex.

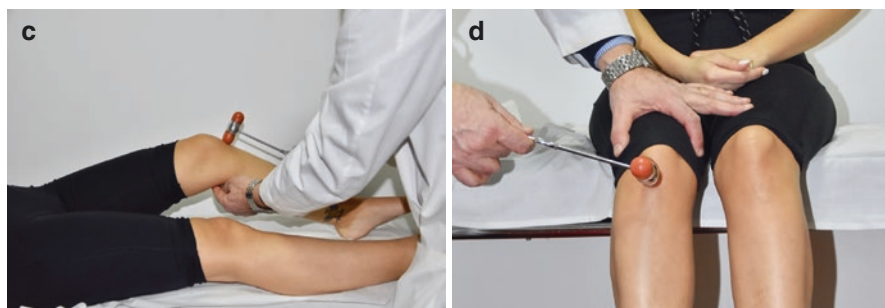


Fig. 1.17 (continued)

1.14 Examination of the Foot & Ankle

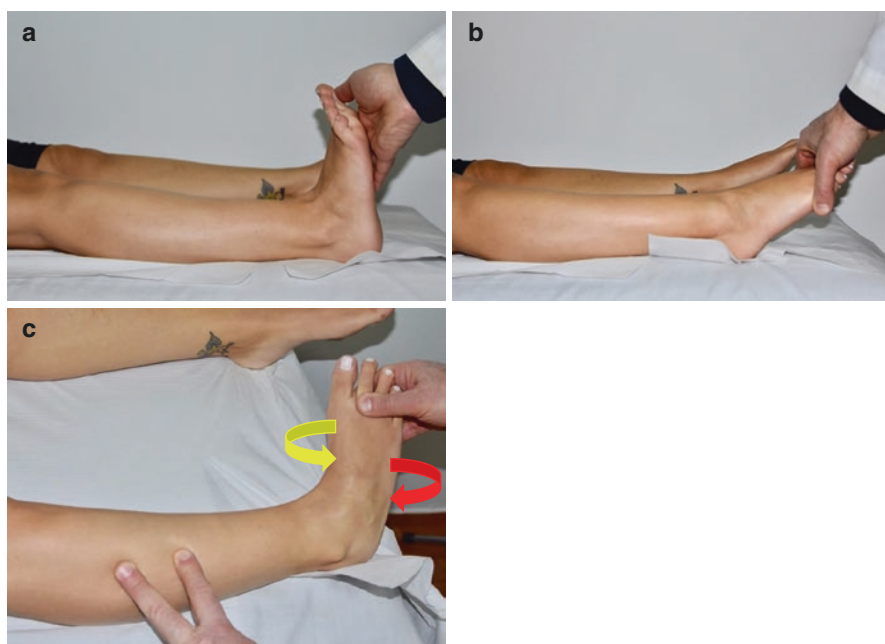


Fig. 1.18 Foot and ankle

Figure 1.18a Flexion.

Figure 1.18b Extension.

Figure 1.18c Inversion and supination (yellow curved arrow). Eversion and pronation (red curved arrow).

The foot and ankle are specially designed to transmit the body's weight. The foot is capable of adjusting to cope with different terrains. The foot and ankle can be involved in different pathologies such as trauma (sprain, fracture), biomechanical defects (pes planus/flat foot), periarticular causes such as plantar fasciitis, retrocalcaneal bursitis, enthesopathies, and finally inflammatory arthritides and OA. Inspect for any deformities, bruises, scars. Primary OA of the ankle is rare. Usually, it appears after injuries. RA may affect the ankle joint. Enthesitis (e.g. tibialis anterior) may manifest as ankle pain and swelling on the medial part of the ankle in patients with psoriatic arthritis (PsA). Assess the ROM. MSUS is a helpful imaging modality.

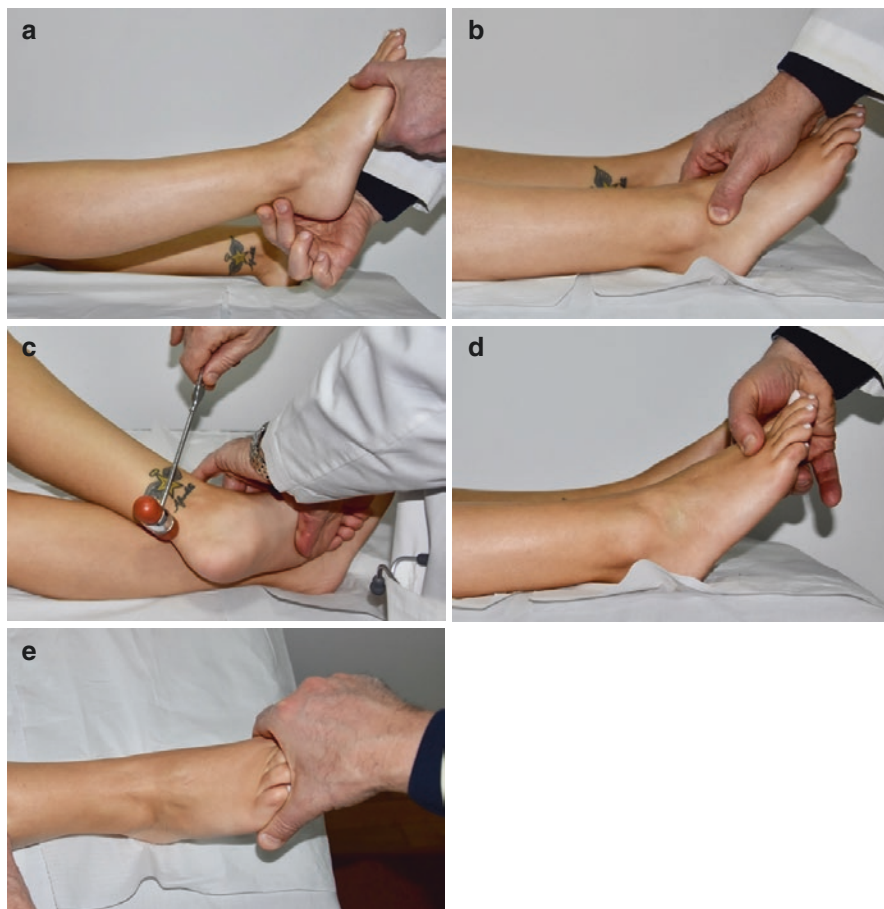


Fig. 1.19 Foot and ankle

Figure 1.19a Palpation of the Achilles tendon.

Figure 1.19b Palpation of the subtalar region.

Figure 1.19c Ankle reflex (Achilles tendon reflex).

Figure 1.19d Palpation of the metatarsals.

Figure 1.19e Squeeze test of the metatarsal heads.

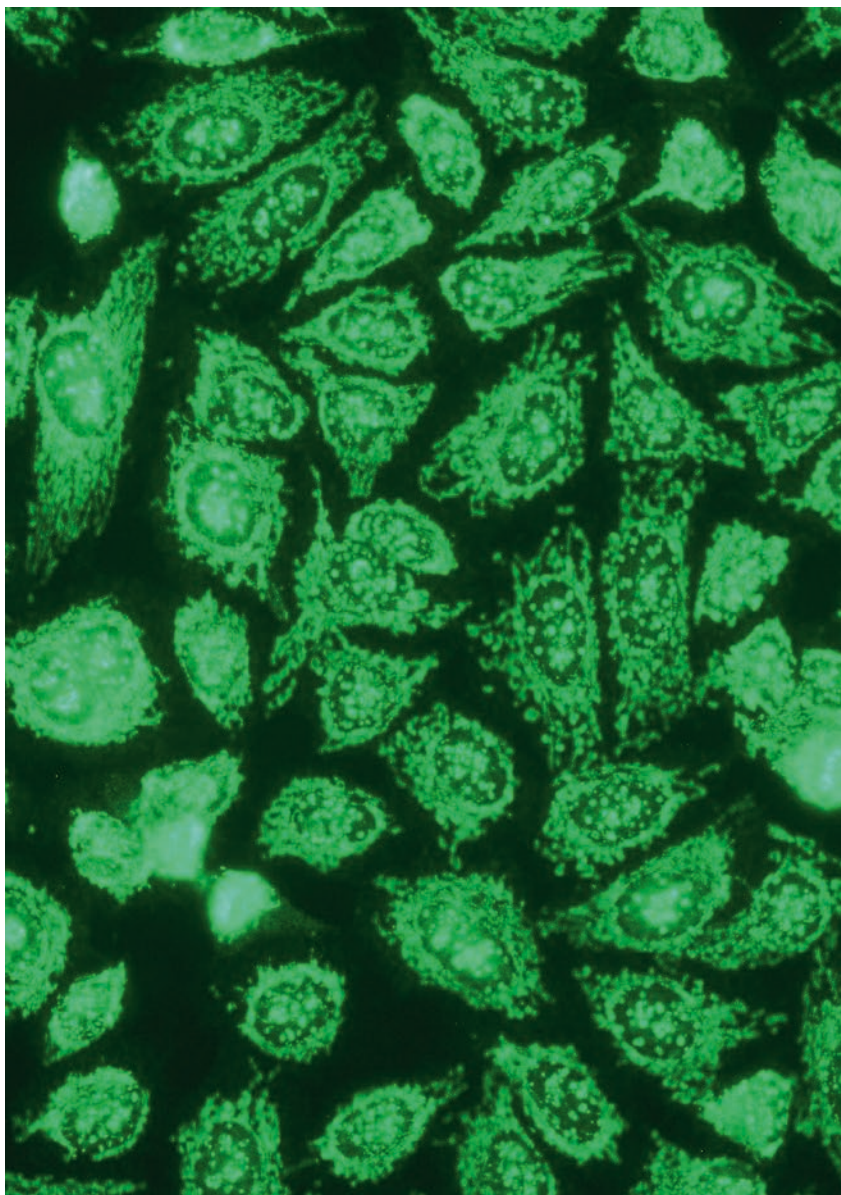
Inspect for any deformities. Pes cavus and pes planus are not so uncommon findings. Look for toe deformities (ie. hammer toes, hallux valgus). The nails of the toes may also be affected (ie. hyperkeratosis, pitting nails in PsA). Palpate the Achilles tendon. Pain in the heel is a common complaint in the middle-aged and may be due to tearing of the calcaneal attachment of the plantar fascia following degenerative changes in its structure. Inflammatory changes in the tendon sheaths behind the malleoli may give rise to pain at the sides of the ankle joint. The tibialis posterior and peroneus longus are most frequently involved. Anterior metatarsalgia may be due to osteoarthritic degenerative changes but it is commonly seen in RA patients. The first metatarsophalangeal (MTP) joint is commonly involved in gout. For a complete lower extremity examination, the clinician should test for the ankle reflex.

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Chapter 2

Laboratory and Immunological Tests in Rheumatology



2.1 Introduction

A wide spectrum of various laboratory and immunological tests are available in the everyday clinical practice for patients with rheumatic diseases. Some tests help physicians in establishing a diagnosis or simply categorising/classifying a suspected disease. Others, demonstrate the extent but also the nature of any pathological changes, while others are necessary to monitor disease activity of an inflammatory disorder and help the physician to assess the therapeutic response.

2.2 Non-specific Laboratory Markers

The inflammatory status in a systemic disease such as rheumatoid arthritis (RA), spondyloarthropathies (SpA) or vasculitis, results in several haematological and biochemical responses. An example is the so called “anaemia of chronic disease” (normocytic, normochromic) with low serum iron and normal or high ferritin levels. Another example is the increased output of several proteins in chronic inflammatory conditions, including the C-reactive protein (CRP), complement components (C3, C4), fibrinogen and others. These proteins contribute to an increased erythrocyte sedimentation rate (ESR) as well as a high blood viscosity. A full blood count (FBC) with differential, ESR and CRP are used routinely to screen patients who may have an inflammatory rheumatic disease. In addition, the haemoglobin, the ESR and the CRP levels can also be used in the everyday clinical practice for an accurate assessment of the disease activity and the response to therapy.

2.3 Specific Laboratory Markers in Rheumatology

An autoimmune rheumatic disease (ARD) is characterised by:

- (a) the presence of serum autoantibodies, or/and autoreactive T-lymphocytes on blood samples,
- (b) by the presence of chronic inflammatory cells in a tissue biopsy of an affected organ consisting mainly by macrophages and lymphocytes, and,
- (c) by the provocation of the disease if serum or blood from patients suffering from an autoimmune disease are injected in animal models.

2.4 Autoantibodies

Rheumatoid Factors (RF) are immunoglobulins of the IgM, IgG or IgA class which react with the Fc component of the human IgG molecule. The commonest used tests are latex and sheep cell agglutination, as well as, nephelometry testing the

IgM-RF. They are found in patients with many ARDs, mainly RA, but also in Sjögren's syndrome (SS), mixed connective tissue disease (MCTD) and others. They are also found in other conditions, especially in chronic inflammatory conditions, liver diseases (hepatitis B and C, cirrhosis), cryoglobulinaemia, infective endocarditis, leishmaniasis and other chronic disorders such as interstitial lung disease.

Anti-citrullinated protein antibodies (ACPA) are immunoglobulins of the IgM, IgG and IgA classes directed against citrullinated peptides. In contrast to RF, these autoantibodies are more specific for RA and play a significant role in its pathogenesis. Citrullination is a reaction mediated by peptidylarginine deiminase (PAD) enzymes which convert the DNA-encoded amino acid arginine to citrulline. This post-translational modification occurs under physiological but also pathological circumstances. Candidate citrullinated peptides can be: fibrinogen, fibronectin, enolase, collagen type II and others. The presence of ACPA in RA patients provide many hypotheses for disease pathophysiology. Many known risk factors may play a role against citrullinated peptides and the formation of ACPA. The formation of these autoantibodies is associated with both genetic and environmental risk factors for RA. Specific human leucocyte antigen (HLA) alleles and smoking are some of them. The HLA-DRB1 *01, *04, and *10 alleles are the suggested genetic risk factors for RA development in particular for ACPA positive RA. Most HLA-DRB1 alleles associated with RA share an identical amino acid sequence in the peptide-binding groove which is called shared epitope (SE). Of the environmental risk factors for ACPA positive RA, smoking plays the most important role. Several theories exist on how smoking might predispose in the development of RA. It seems that smoking leads to higher expression of the PAD-2 enzyme, increasing citrullination in the lungs. In addition, a gene-environment interaction has been reported between HLA-DRSE alleles and to a lesser extent protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene and smoking. This interaction suggests interplay between T-lymphocytes and the abundance of citrullinated antigens, leading to a break of tolerance. These autoantibodies are detected using new generation enzyme-linked immunosorbent assay (ELISA).

Autoantibodies directed against nuclear proteins (ANA) are very common in ARD. These are detected with the use of indirect immunofluorescence (IF). This assay is an ideal screening test for possible connective tissue diseases because of its very good sensitivity (>90% when using human cultured cells as a substrate), and simplicity. Positive ANAs make part of the criteria for the classification of systemic lupus erythematosus (SLE), but their specificity for SLE is low, because they are found in several other connective tissue diseases like MCTD, SS, RA, and others. Also, they can be positive in chronic inflammatory states such as infectious endocarditis, leishmaniasis, hepatitis B and C, liver cirrhosis, interstitial lung disease and other. In contrast to the low positive predictive value of ANA testing, a patient with negative ANA (<1/80) has less than 3% chance of having SLE. Thus, a negative ANA test is useful for excluding the diagnosis of SLE. The ANAs are directed against various antigenic components of the nucleus. DNA, histone proteins, ribonucleoproteins [Ro(SSA), La(SSB), U1RNP, Sm] are some of them. ANA were discovered in 1948 when Hargraves and collaborators reported the lupus cell (LE) in a patient suffering from SLE.

Using as substrate for IF Hep-2 cells, we are able to detect five types or patterns of IF:

- (a) homogeneous or diffuse pattern,
- (b) the speckled pattern,
- (c) the annular or ring pattern,
- (d) the antinucleolar and
- (e) anticentromere patterns which are associated with scleroderma. The other types of ANA, diffuse and speckled are not specific because they are detected in many ARDs. Autoantibodies directed against double-stranded (ds)-DNA and Sm antibodies are found in patients with SLE, while the detection of U1RNP is diagnostic for MCTD. On the other hand, Ro (SSA) and La (SSB) autoantibodies are found in patients with SLE and SS. There are also antibodies against topoisomerase I (Scl 70) and against RNA polymerase III, which are specific for scleroderma.

Antineutrophil cytoplasmic antibodies (ANCA). These are antibodies directed against cytoplasmic components of neutrophil cells. The indirect IF is the screening test for detection of ANCAs. With this method two types of IF were identified. A cytoplasmic IF pattern named c-ANCA and a peri-nuclear IF pattern called p-ANCA. Multiple antibodies may lead to positive tests for c- or p-ANCA. However, only antibodies to proteinase-3 (PR-3) and myeloperoxidase (MPO) are associated with ANCA associated vasculitides (AAV). AAV include microscopic polyangiitis (MPA), Wegener's granulomatosis (WG) or granulomatosis with polyangiitis (GPA) and Churg-Strauss syndrome or eosinophilic granulomatosis with polyangiitis (EGPA). A positive ANCA test, must be followed by the detection of PR3 or MPO using the ELISA method. False-positive ANCAs may be seen in various chronic diseases such as inflammatory bowel disease or infections. In these instances, the recognised cytoplasmic proteins are other than PR3 or MPO such as lactoferrin or other cytoplasmic neutrophil compounds.

Antiphospholipid antibodies (aPLs) are antibodies directed against negatively charged phospholipids. They include the lupus anticoagulant (LA), the anticardiolipin antibodies (aCL) and the anti-b2 glycoprotein I antibodies (β 2-GPI). The LA behaves as a prothrombotic agent *in vivo*. To confirm the presence of LA the following criteria are required:

- (a) a sensitive screening test must show prolongation of the clotting time (activated partial thromboplastin time – aPTT) or the dilute Russell's viper venom time (dRVVT),
- (b) prolongation of the clotting time may be due to an inhibitor. This is confirmed by demonstration that the prolonged clotting time does not correct when it is mixed with normal plasma,
- (c) phospholipid dependence of the coagulation test must be demonstrated.

aCL is an antibody directed against negatively charged phospholipids bound to β 2-GPI. Anti- β 2-GPI is another antibody against this glycoprotein. aCL and anti- β 2GPI, are detected using sensitive ELISA. These aPL antibodies are found in patients with SLE and antiphospholipid syndrome (APS), but also in many chronic inflammatory diseases and infections.

The *complement* and *cryoglobulins* are other tests useful in ARDs. The complement is an acute phase reactant produced by the liver in chronic inflammation and infections. Complement has no diagnostic value except those cases where the C3 or C4 complement components are low. This could indicate a disease with immune complexes (ICs) such as systemic vasculitis or lupus nephritis. *Cryoglobulins* (cryo) are proteins that have the potential to precipitate upon exposure to cold. They are thought to represent circulating ICs and may be associated with many different vasculitic syndromes including AAV, RA vasculitis etc. They may also occur in patients with chronic infections like hepatitis C and B. There are three types of cryoglobulinaemia:

- (a) type I cryoglobulinaemia, or simple cryoglobulinaemia, is the result of a monoclonal immunoglobulin, usually immunoglobulin M. This type is more frequent in haematological disorders like multiple myeloma, Waldenstrom disease,
- (b) type II or mixed monoclonal cryoglobulinaemia, consists of ICs which contain a monoclonal immunoglobulin with RF reactivity and a polyclonal immunoglobulin. This type can be found in haematological disorders as well as in patients with SLE, SS and other ARDs. Finally,
- (c) type III or mixed polyclonal cryoglobulinaemia consists of ICs and contain polyclonal immunoglobulins with RF reactivity.

Types II and III cryoglobulinaemia represent 80% of all cryoglobulins.

Tissue typing for HLA antigens has a limited role as a diagnostic tool, especially where the disease and HLA concordance is not high. However, the absence of a particular antigenic type may provide useful information in a case where the diagnosis is in doubt on clinical grounds. However, a number of different diseases have been found to be associated to a variable degree with particular HLA antigens. An example is the association of HLA-B27 with ankylosing spondylitis (AS), where individuals positive for this tissue type have more than 90% chances to develop AS, than HLA B27 negative subjects. Another example is the presence of HLA-DRB1 alleles associated with seropositive RA which has a bad prognosis.

2.5 Nuclear Patterns

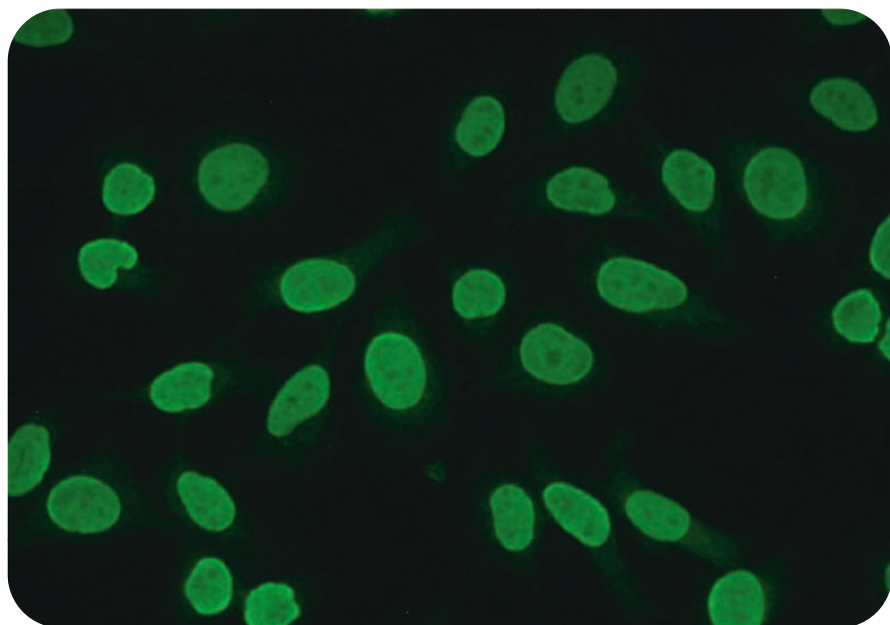


Fig. 2.1 Homogeneous pattern (diffuse)

A uniform diffuse fluorescence of the entire nucleus of interphase cells. The fluorescence associates with the condensed chromatin in mitotic cells, where it is often more pronounced. The surrounding cytoplasm is negative. High titre samples and poorly prepared or aged substrates may show more pronounced staining at the outer rim of interphase nuclei (homogeneous with nuclear rim. *See also Fig. 2.5*).

Disease association:

Systemic lupus erythematosus
Drug-induced lupus
Juvenile idiopathic arthritis
Systemic sclerosis

Antigen association:

ds-DNA
Nucleosomes
Histones

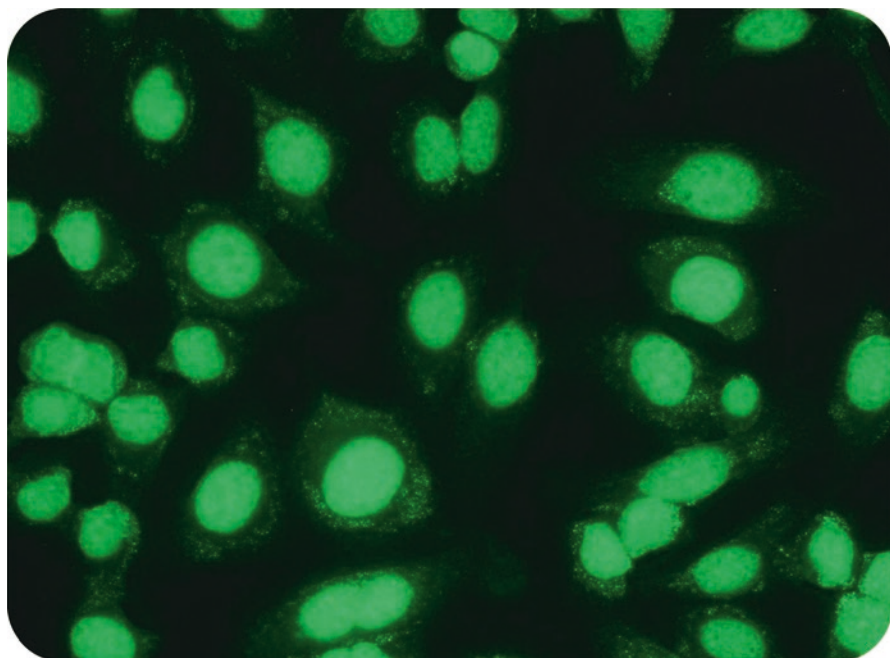


Fig. 2.2 Fine speckled pattern (granular)

Fine to discrete speckled staining of interphase nuclei in a uniform distribution. Cells in mitosis show no staining of the condensed chromosomal region. Frequently found in association with other nuclear autoantibodies which may convert the pattern to nuclear homogeneous.

Disease association:

Systemic lupus erythematosus
Sjögren's syndrome
Systemic sclerosis
Myositis
Mixed connective tissue disease

Antigen association:

Ro (SSA)
La (SSB)
Mi-2
TIF1 γ
TIF1b
Ku

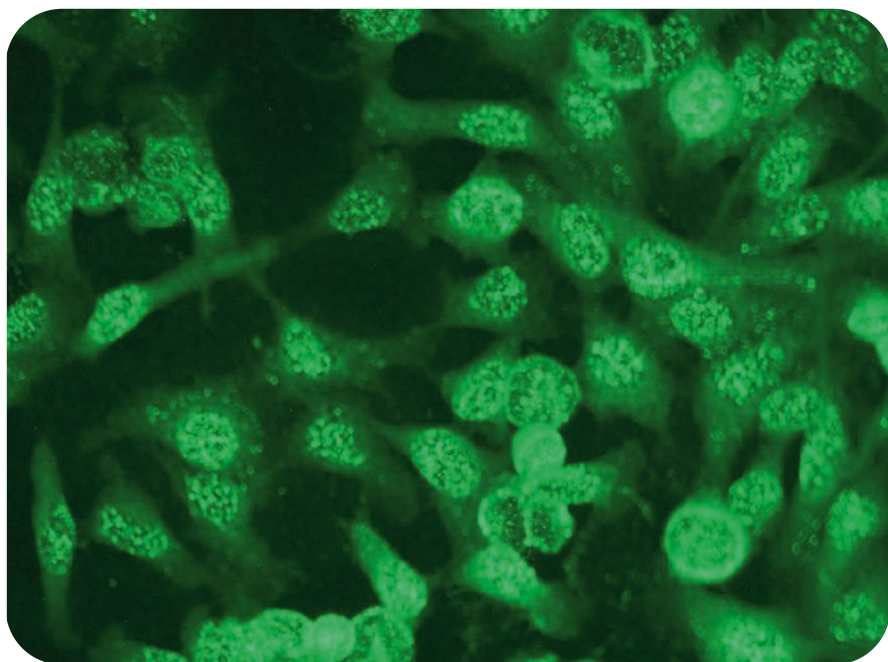


Fig. 2.3 Coarse speckled ANA pattern – Nuclear matrix

This is an example of a speckled ANA pattern called Nuclear matrix. Variable large speckles, excluded from the nucleoli, in a sponge-like nuclear network. Cells in mitosis show no staining of the condensed chromatin (not shown in this figure).

Disease association:

Mixed connective tissue disease
Systemic lupus erythematosus
Systemic sclerosis
Rheumatoid Arthritis

Antigen association:

hnRNP
U1RNP
Sm
RNA polymerase III

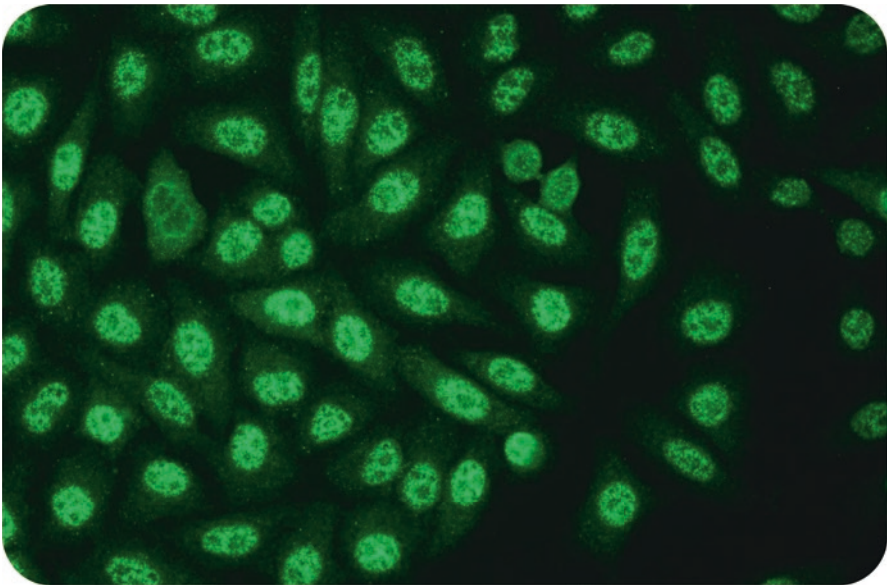


Fig. 2.4 Coarse speckled
Dense, intermediate sized particles in interphase nuclei together with large speckles. Cells in mitosis show no staining of the condensed chromosomal region. The clinical association varies depending upon the antigenic target. U1-small nuclear RNP (U1-snRNP) and Sm autoantibodies are markers for MCTD and SLE respectively. U2-snRNP autoantibodies are reported in systemic sclerosis – polymyositis overlap, SLE, MCTD, Raynaud’s phae-nomenon (RP) and psoriasis. U4/U6-snRNP autoantibodies have been described in patients with SS and systemic sclerosis (*See also* Fig. 2.3).

<p>Disease association:</p> <p>Mixed connective tissue disease</p> <p>Systemic lupus erythematosus</p> <p>Systemic sclerosis</p> <p>Rheumatoid Arthritis</p>	<p>Antigen association:</p> <p>hnRNP</p> <p>U1RNP</p> <p>Sm</p> <p>RNA polymerase III</p>
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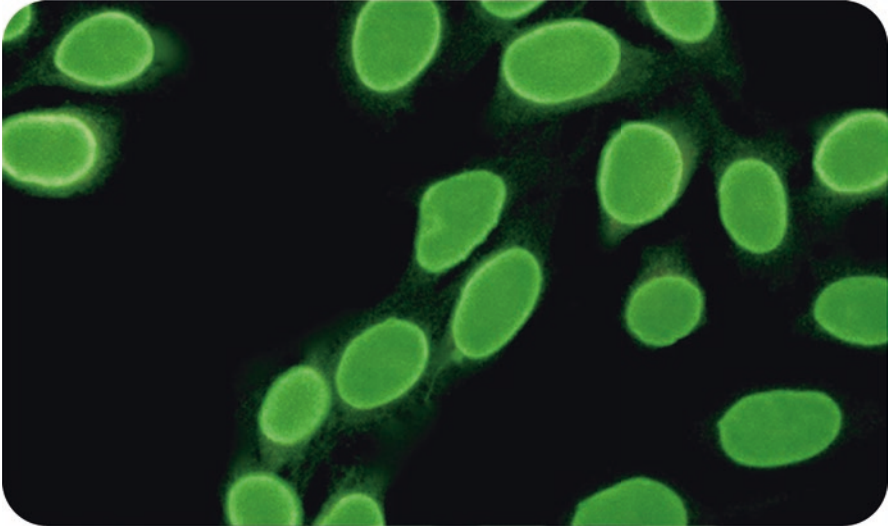


Fig. 2.5 Rim/Peripheral

Autoantibodies against nuclear membrane show a fine, linear fluorescence pattern of the nuclear membrane with less intense homogeneous staining of the entire nucleus. It is a uniform diffuse nuclear staining with greater intensity at its outer rim. Peripheral patterns are more frequently found when rodent tissue sections are used as substrates. This is a rare ANA pattern and can be detected in the sera of overlapping autoimmune disorders such as hepatitis and cholangitis and is variably associated with vasculitis, thrombocytopenia, as well as SLE.

Disease association:

Systemic lupus erythematosus
Overlapping autoimmune disorders
Low-titer antibodies have been also
observed in patients with chronic fatigue
syndrome

Antigen association:

GP210
Lamin A
Lamin B
Lamin C
Lap 1A
Lap 2

2.6 Cell Cycle Patterns

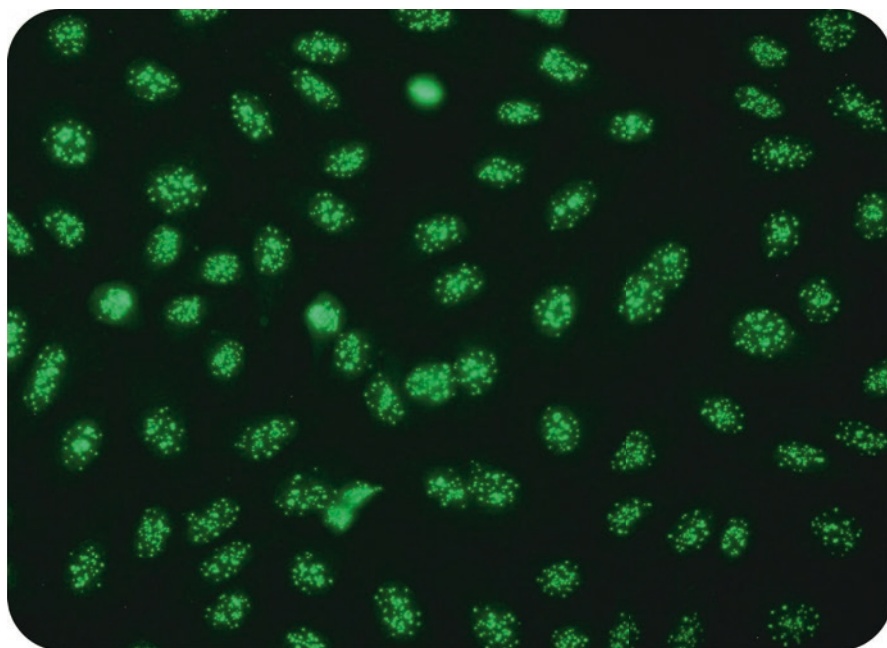


Fig. 2.6 Centromere pattern

Forty–sixty discrete speckles distributed throughout the interphase nuclei and characteristically found in the condensed nuclear chromatin during mitosis as a bar of closely associated speckles. It is primarily found in limited sclerosis or CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasias), a mild variant of progressive systemic sclerosis of which approximately 55% are anti-centromere antibody (ACA) positive. Sera from patients with primary biliary cirrhosis, RP and infrequently SS can also be ACA positive.

Disease association:

Limited cutaneous systemic sclerosis
Primary biliary cirrhosis
Sjögren's syndrome

Antigen association:

CENP-A
CENP-B
CENP-C

2.7 Nucleolar Patterns

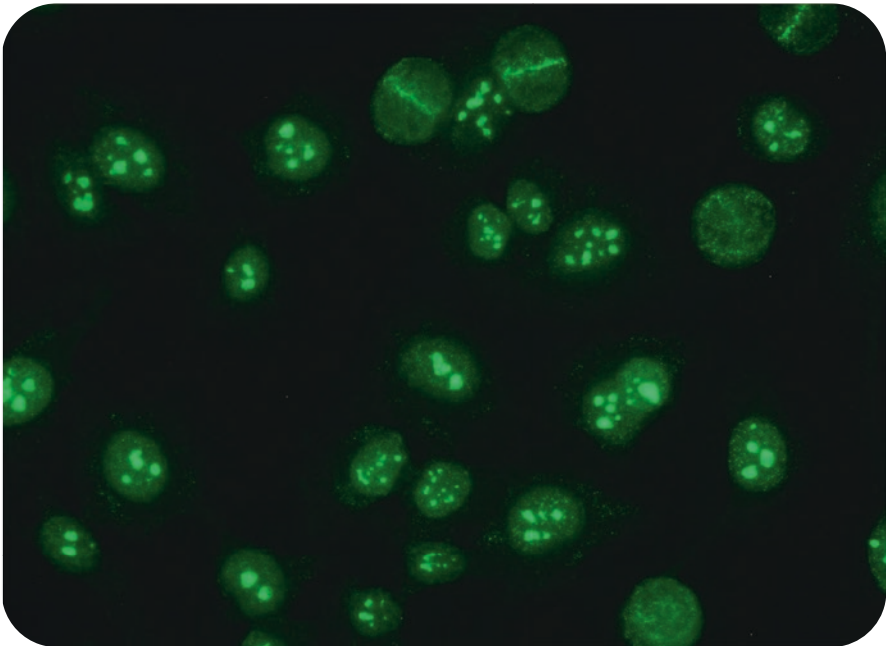


Fig. 2.7 Nucleolar homogeneous pattern
Homogeneous staining of the nucleoli associated with weak homogeneous or speckled staining of the nucleoplasm. Diffuse cytoplasmic staining is seen in mitosis without fluorescence of the condensed chromosomal region. This pattern is found in 25–50% of patients with myositis – scleroderma overlap syndrome and less frequently in the individual diseases (approximately 3% systemic sclerosis and 8% myositis).

<p>Disease association:</p> <p>Systemic sclerosis / myositis overlap</p> <p>Systemic sclerosis</p> <p>Myositis</p>	<p>Antigen association:</p> <p>PM / Scl-75</p> <p>PM / Scl-100</p> <p>Th/To</p> <p>B23 / nucleophosmin</p> <p>Nucleolin</p> <p>No55/SC65</p>
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2.8 Cytoplasmic Speckled Patterns

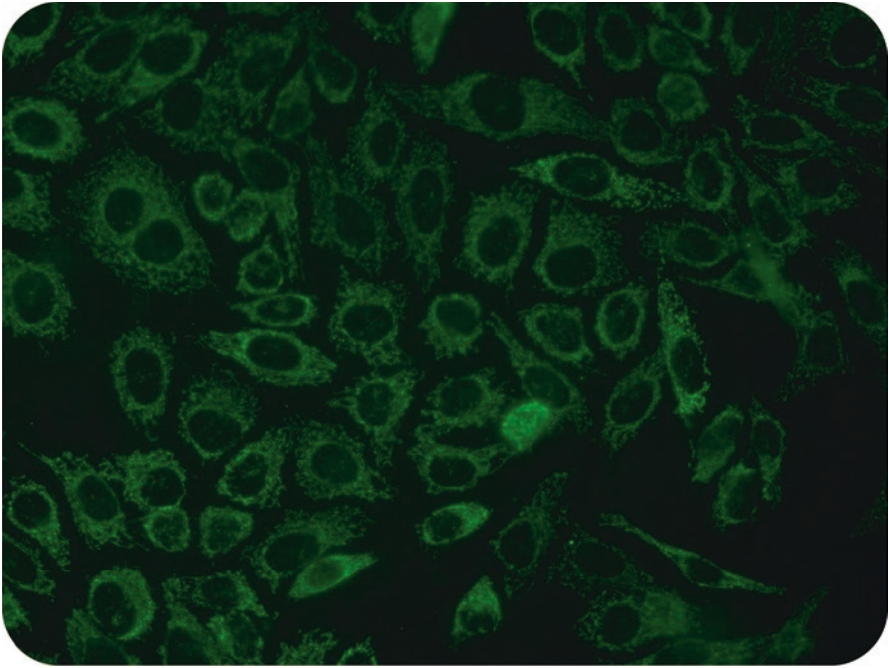


Fig. 2.8 Mitochondrial

Granular filamentous staining extending around the nucleus and throughout the cytoplasm. Rodent liver, kidney, stomach sections are useful for the detection of anti-mitochondrial antibodies due to the distinct staining pattern on each tissue. For patients with primary biliary cirrhosis (PBC), an M2 ELISA should be used to confirm a positive test.

Disease association:

Primary biliary cirrhosis
Systemic sclerosis
Systemic lupus erythematosus
Sjögren's syndrome

Antigen association:

M2

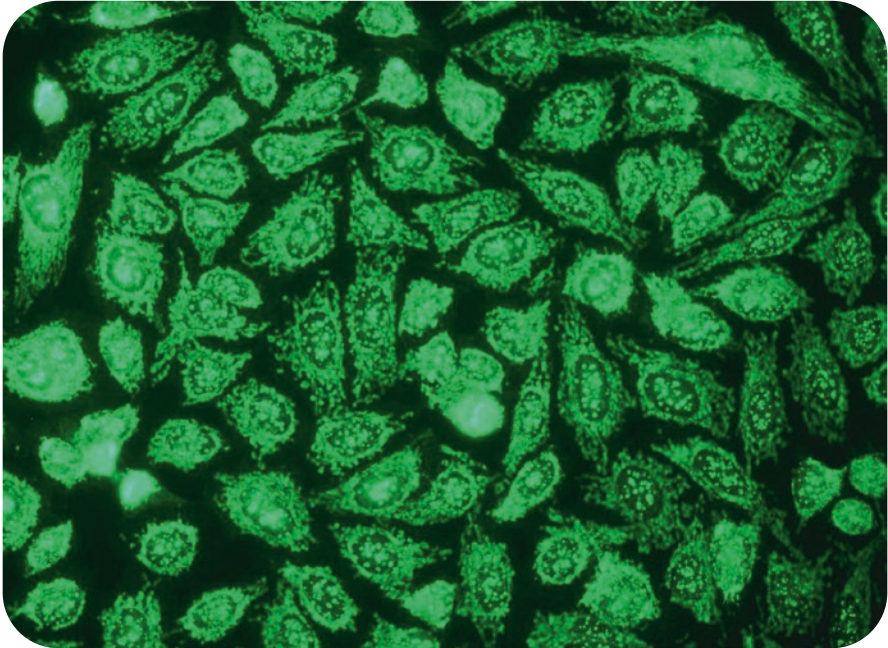


Fig. 2.9 Mitochondrial staining and centromere pattern

Sometimes more than one patterns can be present. In this figure, granular filamentous staining extending around the nucleus and throughout the cytoplasm as well as discrete speckles distributed throughout the interphase nuclei.

Disease association:

Primary biliary cirrhosis
Limited systemic sclerosis

Antigen association:

Not specific

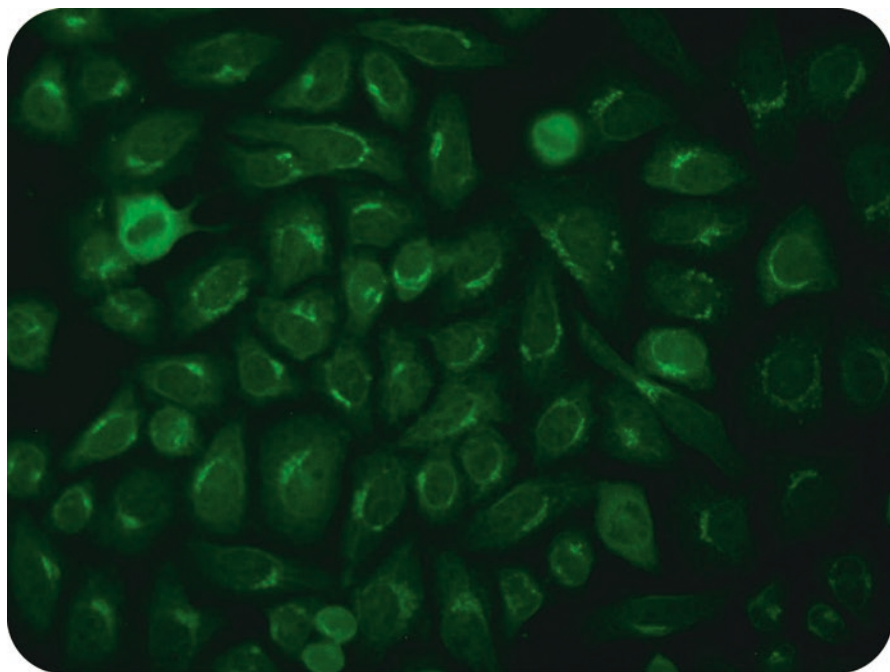


Fig. 2.10 Golgi apparatus

Golgi complex consists of a speckled staining installed to one part of the nucleus, composed by large granules. This is a rare pattern found in patients with chronic rheumatic diseases.

Disease association:

Sjögren's syndrome
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed-connective tissue disease

Antigen association:

Giantin / macrogolgin
Golgin-95 / GM130
Golgin-160

2.9 ANCA Patterns

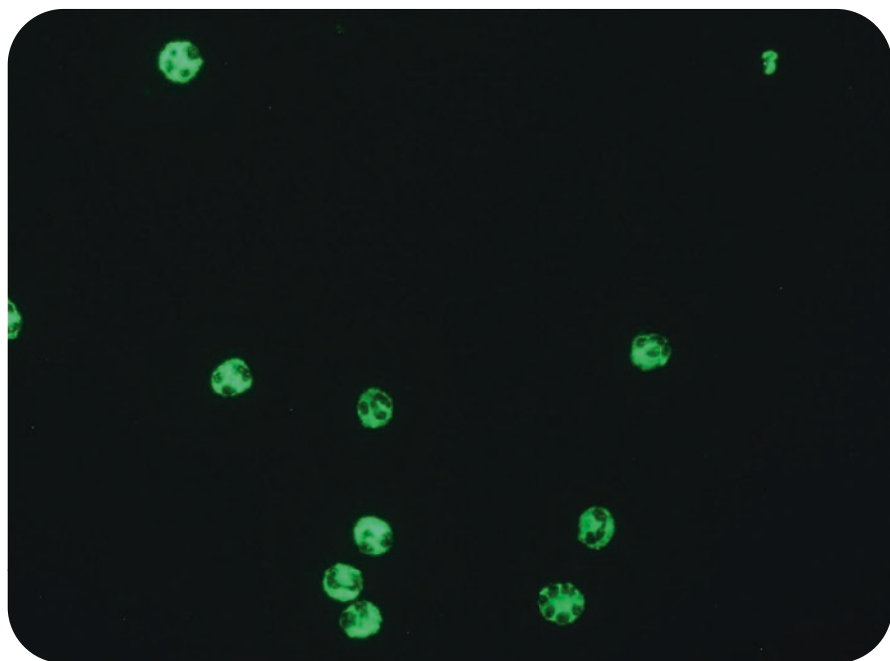


Fig. 2.11 c-ANCA pattern

Ethanol-fixed neutrophils stained with anti-PR3 antibodies, producing the characteristic c-ANCA pattern of cytoplasmic granular fluorescence with interlobular accentuation. The target PR-3 is serine protease found in the azurophilic granules of neutrophils and in peroxidase-positive lysosomes of monocytes.

Disease association:

Granulomatosis with polyangiitis
Microscopic polyangiitis
Eosinophilic granulomatosis with
polyangiitis
Ulcerative colitis
Rheumatoid arthritis (rare)

Antigen association:

Proteinase-3

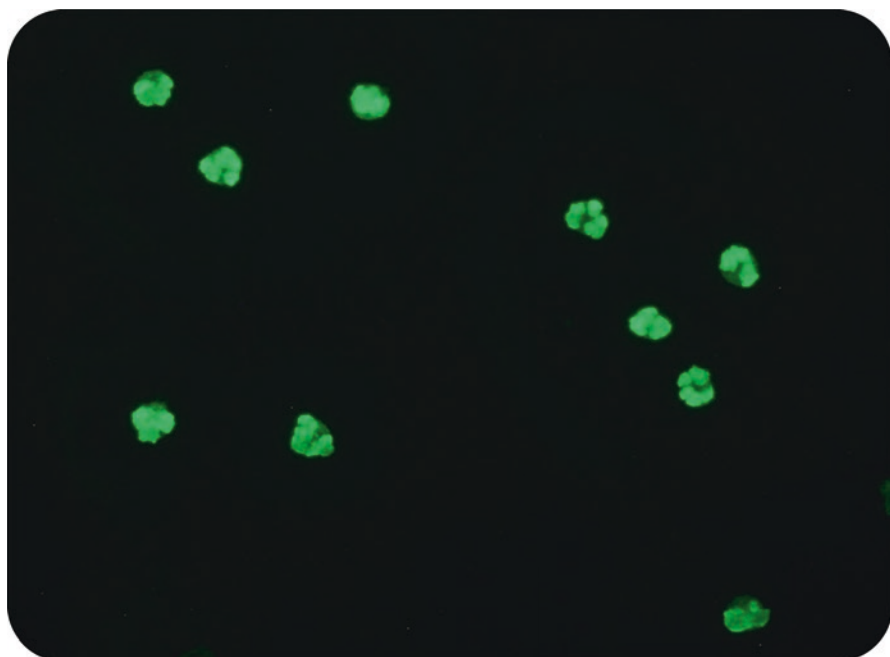


Fig. 2.12 p-ANCA pattern

Ethanol-fixed neutrophils stained with anti-MPO antibodies, producing the characteristic p-ANCA pattern of perinuclear fluorescence with nuclear extension. The target antigen of anti-MPO antibodies is MPO, a covalently-linked dimer found in the positively charged azurophilic granules of neutrophils and lysosomes of monocytes.

Disease association:

Microscopic polyangiitis
Primary pauci-immune necrotising
crescentic glomerulonephritis
Eosinophilic granulomatosis with
polyangiitis
Granulomatosis with polyangiitis

Antigen association:

Myeloperoxidase

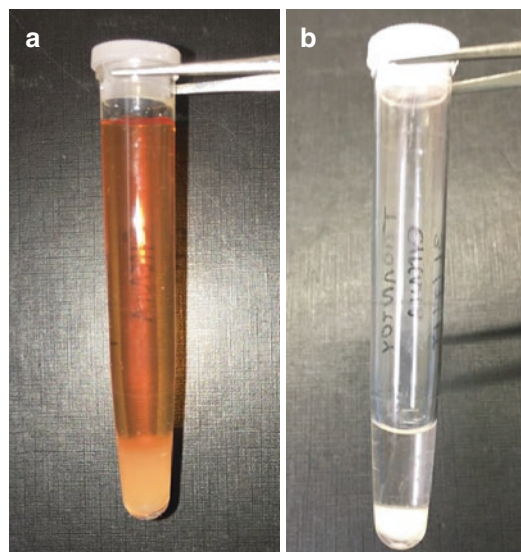


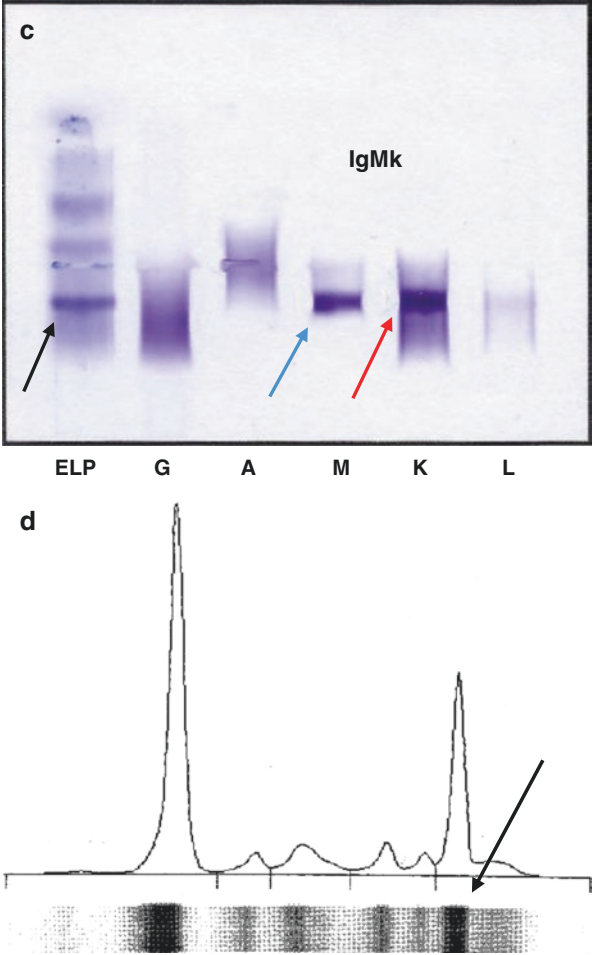
Fig. 2.13 Serum protein electrophoresis (ELP) and Cryoglobulins (Cryo)

Cryo are special serum immunoglobulins that precipitate at temperatures mostly at 0–4 °C, and dissolve when re-warmed to 37 °C. Cryoglobulinaemias are caused by an abundance of proteins called cryo in the blood.

Semi-quantitative detection of cryo by cryocrit. The cryocrit is a simple and widely used method. A special conical tube is filled with 10 ml of serum and left in a refrigerator for 7 days (Fig. 2.13a). The tube is centrifuged and the precipitate can then be washed and analysed further. The precipitate is gently washed 3 times with 2 ml of ice-cold saline solution, without disturbing the precipitate, followed by centrifuging at 4 °C for 10 min. The cryo precipitate is dissolved in 1 ml of warm (37 °C) saline solution overnight for qualitative/quantitative analysis (Fig. 2.13b). Qualitative analysis of serum protein was performed with ELP and immunofixation (Fig. 2.13c). Quantitative analysis was performed with the measurement of immunoglobulins, C4 and the rheumatoid factor.

In the left column a serum protein ELP is shown. You can notice a dense band (protein) in the region of γ (gamma) – globulins (black arrows). To identify this protein an immunoelectrophoresis with immunofixation is done. Thus, specific IgG, IgA, and IgM antibodies are applied to identify this dense band. You can also notice that this band is recognised by the IgM (blue arrow). Then the light chains κ (kappa) λ (lambda) are also applied. As you notice, this band is recognised by κ light chain (red arrow). Thus, this band shown in the ELP is a paraprotein consisting of IgM κ monoclonal protein. In Fig. 2.13d, a serum protein ELP is shown with a monoclonal protein in the region of γ -globulins.

Fig. 2.13 (continued)



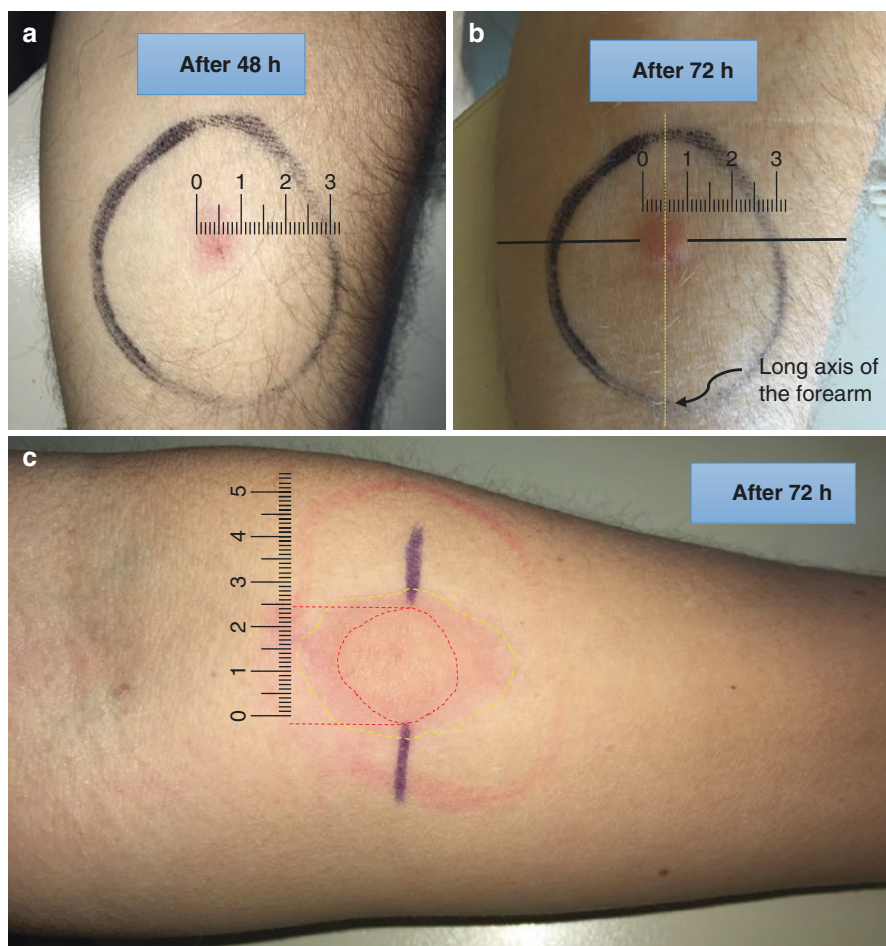


Fig. 2.14 Purified protein derivative tuberculin or Mantoux test

Mantoux testing or skin testing with tuberculin is most widely used to identify latent tuberculosis infection in a rheumatology patient prior of initiating a treatment with a biologic agent. It is recommended that tests should be read at 48 or 72 h after injection by a health-care professional. It is crucial to measure only the induration (palpable, raised, hardened area or swelling) and not the erythema (redness of the skin). Moreover, the diameter of the indurated area should be measured across the forearm in millimeters (mm).

In Fig. 2.14a, an erythema is only seen after 48 h of the injection which became a hard and swollen area of 10 mm after 72 h (Fig. 2.14b). In Fig. 2.14c, a positive Mantoux test is seen of 25 mm induration (red dashed circle). The redness of the skin is approx. >30 mm (yellow dashed circle) and should not be measured.

Category	Visual	Viscosity	Cell count
Normal	Colorless – straw clear	High	<150 leucocytes (<25% neutrophils)
Non-inflammatory	Yellow – slightly cloudy	Decreased	<1000 leucocytes (<30% neutrophils)
Inflammatory	White, yellow cloudy, turbid	Absent	<100,000 leucocytes (>50% neutrophils)
Septic	White, gray, yellow/green, cloudy, purulent	Absent	50,000–200,000 leucocytes (>90% neutrophils)
Crystal induced	White, cloudy, opaque, turbid, milky	Absent	500–200,000 leucocytes (<90% neutrophils)
Haemorrhagic	Xanthochromic, red	Absent	50–10,000 leucocytes (<50% neutrophils)

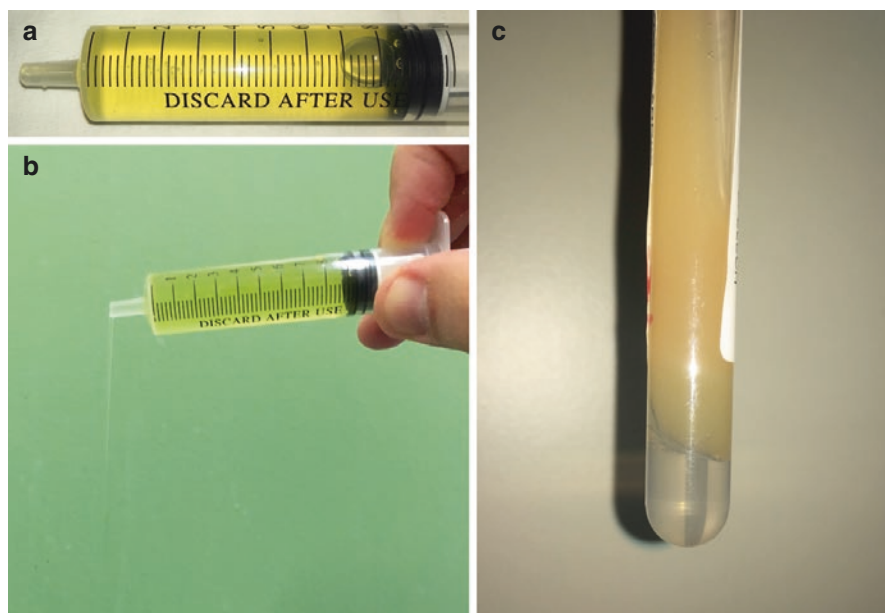


Fig. 2.15 Synovial fluid analysis

Joint fluid or synovial fluid (SF) analysis is a very helpful examination for the rheumatologists in their everyday clinical practice in order to diagnose joint disease. The etymology of the word comes from the Greek word “syn – with” and the Latin “ovum – egg”, as SF resembles the white of an egg. SF is a viscous, mucinous substance that lubricates most joints. The colour of the SF is depicted in Fig. 2.15a whereas the viscosity or string test is shown in Fig. 2.15b. In Fig. 2.15c, SF of a patient with septic arthritis is shown. Laboratory parameters that can be measured are the volume, colour, clarity, and viscosity of the fluid. Proteins, glucose, uric acid, lactic acid, lactate dehydrogenase and RF can also be measured. Finally, microscopic examination of the SF can give valuable information and can confirm a presumptive diagnosis (*see the above table*).

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Chapter 3

Rheumatoid Arthritis



3.1 Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease that is characterised by progressive joint disorder with significant pain and stiffness, which lead to functional disability and systemic complications if left untreated. The direct (health care costs) and indirect (productivity loss) socioeconomic costs of the disease are of major significance. The first evidence of RA was noted in radiological examination of skeletal remains of Tennessee Indians from as early as 4500 BC. The term “rheumatism” dates back to 1630 but in 1859, a physician named Alfred Garrod used the term “rheumatoid arthritis” to describe the disease as we know it today.

3.2 Epidemiology

The prevalence of RA ranges from 0.5% to 1.0%, although there are populations with reported prevalence as high as 6.8% (Chippewa Indians) and populations with very low prevalence 0.2–0.3% (Japan and China respectively). The incidence of RA increases with increasing age in most populations until the eighth decade of life, when it declines. A female to male ratio is about 3:1. Although RA is more common in women than in men in all age groups, the sex difference is more obvious at a younger age.

3.3 Risk Factors

The risk factors that have been linked to RA include, a positive family history, smoking (this is particularly strong for people who are anti-citrullinated peptide antibody - ACPA positive), environmental exposures (e.g. infections), obesity, age (40–60 years), and sex (women are more likely to develop RA as discussed in the section “epidemiology”).

3.4 Signs and Symptoms

Not all the patients will have the same course of the disease. Most patients will have a gradual onset of joint symptomatology over weeks to months. Some of them will have a waxing and waning course of the disease for months to several years, named as palindromic rheumatism. Others, may develop an acute form with the classic joint stiffness, pain, and swelling accompanied by systemic symptoms, such as malaise, fatigue and weakness.

Articular manifestations include morning stiffness that is more prominent in the morning or after long periods of inactivity. Symmetrical polyarthritis involving the proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs), wrists, elbows, shoulders, hips, knees, ankles, and metatarsophalangeal joints (MTPs) are the clinical hallmark of RA. The hands and wrists are commonly affected (90%). Joint tenderness and swelling are the main clinical findings at the beginning, but typical joint deformities (ulnar drift at the MCPs, rotatory subluxation at the wrist, swan-neck and boutonniere deformities) appear over time. Osteoporosis can develop leading to fractures.

Extra-articular manifestations affect the skin (subcutaneous nodules that occur mostly in rheumatoid factor (RF) positive patients and it is a marker for severe disease), heart (posterior pericardial effusion, mitral valve prolapse, mitral valve thickening, aortic root dilatation, aortic valve thickening, myocarditis, endocarditis and arrhythmias), lungs (pleural effusions, interstitial pulmonary fibrosis, pulmonary rheumatoid nodules (RN), usual interstitial pneumonitis (UIP), bronchiolitis obliterans with patchy organising pneumonia, lymphoid hyperplasia, and cellular interstitial infiltrates), eyes (scleritis, episcleritis), haematologic effects (anaemia of chronic disease, large granular lymphocyte syndrome, thrombocytopenia), blood vessels (vasculitis which can be localised or systemic).

3.5 Diagnosis and Differential Diagnosis

As there are no diagnostic tests for RA diagnosis, a combination of clinical symptoms and signs but also laboratory tests are used to make its diagnosis. The 1987 American College of Rheumatology (ACR) classification criteria had previously used to define RA. However, as they were developed in patients with longstanding disease they do not apply for patients with early onset RA. In a systematic review the sensitivity and specificity of the 1987 ACR criteria in early RA was 77% and 77% respectively. The relatively low specificity criteria mean that other conditions such as post-viral arthritis, early spondyloarthropathies (SpA) or systemic autoimmune diseases or other self-limited arthritides may satisfy the ACR criteria. Thus, an initiative collaboration between ACR and the European League Against Rheumatism (EULAR) was developed for new classification criteria for RA. The emphasis of these new 2010 ACR-EULAR classification criteria is to identify early RA patients who will benefit from early treatment. These criteria are based on achieving a total score of ≥ 6 (out of 10) from individual scores in four domains. A) number and site of involved joints (score range 0–5), B) serological abnormalities regarding RF and ACPA (score range 0–3), C) raised acute phase reactants, regarding C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (score range 0–1), and D) symptoms duration, regarding disease duration (score range 0–1). While joint symptoms predominate early in RA, other conditions may present with the same features.

These include seronegative SpA, systemic lupus erythematosus (SLE), systemic sclerosis (SCL), mixed-connective tissue disease (MCTD) and Sjögren's syndrome (SS). However, in these conditions other extra-articular manifestations predominate and may precede the joint symptoms like psoriasis, photosensitivity, malar rash, Raynaud's phenomenon (RP) and keratoconjunctivitis sicca (KCS). Thus, a detailed past medical and family history and a complete physical examination will help physicians to recognise the above conditions and to differentiate them from early RA.

3.6 Diagnostic Modalities

Imaging: conventional radiography, magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS) are the three more commonly used imaging modalities in rheumatology. Plain radiography especially on the hands and feet, can give valuable information to the clinician being able to differentiate some types of arthritis. Therefore, it assists in diagnosis, can track disease progression and evaluate response to treatment. Early x-ray findings include soft tissue swelling and the development of periarticular osteopenia. The characteristic bony changes include marginal erosions, subchondral cyst formation, juxta-articular osteopenia, subluxation and dislocation and ankylosis in severe cases. MRI is better than conventional radiography and may show erosions earlier than plain films. MRI can also assess complications such as tendon tear or rupture, synovitis, tenosynovitis, bursitis, erosions, cysts and fibrocartilage degeneration. MSUS is constantly gaining ground because it is a relatively cheap tool in the hands of an experienced rheumatologist that can differentiate inflammatory vs non-inflammatory arthritis, synovitis and bursitis.

Laboratory: RF and ACPA autoantibodies are both diagnostically and prognostically useful, with ACPA to be positive even years before the onset of the disease. Antinuclear antibodies (ANA) can also be present in RA patients. Other commonly associated laboratory findings with RA are anaemia and thrombocytosis, elevated ESR and CRP. CRP may also be used to follow disease activity and response to medication.

3.7 Pathophysiology

RA is a heterogeneous disease, which is based on the data combining genetics, environmental risk factors and autoantibodies. RA can be sub classified into seropositive (ACPA positive) and seronegative (ACPA negative). ACPA are highly

specific for RA, while RF can be found in many autoimmune rheumatic diseases (ARDs) and other conditions. Thus, RA development is the interaction of genetic predisposition [human leucocyte antigen (HLA) and non-HLA] and environmental factors such as smoking and infections. Genetic and environmental determinants interact to create an adverse immune state, which may include the generation of circulation of ACPA. These probably involve the innate immune system (CD4⁺ T-cells, Th-1, Th-2, Th-17 cells, B-cells and macrophages) with further interaction between them with the production of cytokines, chemokines complement activation and recruitment of effector cells, leading to cartilage degradation and joint destruction.

3.8 Management

Lifestyle: dietary interventions have not shown any convincing evidence of benefit for the disease in sine, but because RA patients present usually cardiovascular and other complications, it is advised to use a balanced diet. On the other hand, exercise and physical therapy have promising effects improving quality of life. Finally, advise to stop smoking is an imperative.

Medical Treatment: the key to successful management of RA are early diagnosis and treat to target strategies in order to achieve low disease activity. Corticosteroids (CS) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are the first step to overpower the disease. Biologic agents are reserved for patients with csDMARD intolerance or insufficient response. Methotrexate (MTX) is the first-choice treatment for active RA. Leflunomide (LEF) may be used as an alternative to MTX. Hydroxychloroquine (HCQ) is recommended in patients with low disease activity and in absence of poor prognostic features such as seronegative, non-erosive RA. Sulphasalazine (SSZ) is also used. If monotherapy fails, combination therapy (with two or even three csDMARDs) should be initiated. Tumour necrosis factor (TNF)-inhibitors are the first biologic therapeutic choice in those with poor outcomes on csDMARDs and additional biologic therapies (e.g. the interleukin (IL)-6 inhibitor tocilizumab, the cytotoxic T-lymphocyte antigen (CTLA)-4 inhibitor Abatacept, CD20 inhibitor rituximab) should be considered if there are still poor results.

Surgical Treatment: advanced RA may produce deleterious effects on different joints, usually the hip and knee. Joint replacement is indicated when patients cannot cope with their everyday activities. Long-term outcomes are generally good.



Fig. 3.1 Early rheumatoid arthritis

A 30-years old female with morning stiffness and pain of the small joints of the hands, lasting for more than 7 weeks. In this case there is marked soft tissue swelling involving both wrists, MCPs and all PIP joints. The digits have a fusiform appearance with vasoactive changes. This is a typical case of early RA with symmetrical involvement of both hands affecting the wrists, MCPs and PIP joints.



Fig. 3.2 Elderly-onset or late-onset rheumatoid arthritis

A 65-years old housewife presented swelling, pain and morning stiffness on both hands six weeks earlier. Note the symmetrical involvement and soft tissue swelling of the wrists, MCPs and PIPs bilaterally. This is a late-onset RA.

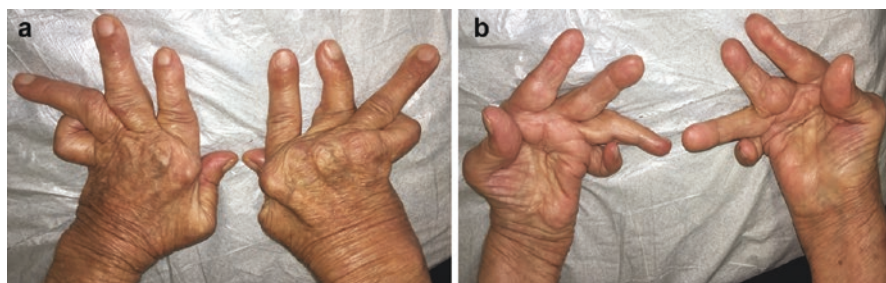


Fig. 3.3 Advanced rheumatoid arthritis – hands

Complete disorganisation of the hand joints. With more advanced disease, MCP subluxation and ulnar deviation of the fingers occur. Boutonniere and swan-neck deformities are also present (*see next figures for more details*). Figure 3.3a and b show the dorsal and volar aspect respectively.



Fig. 3.4 Bilateral ulnar deviation

Ulnar deviation is a common deformity in RA patients which is due to chronic synovitis and erosive changes affecting the MCP joints. Advanced RA with symmetrical ulnar deviation affecting all the MCP joints. Note that the knuckles are prominent due to subluxed MCPs. Ulnar deviation of the MCP joints is a common finding in established RA (Fig. 3.4a). This is a male patient with ulnar drift and thenar eminence atrophy bilaterally which has resulted from damage of the medial nerve caused by the pressure from the inflammatory synovitis of the wrist (Fig. 3.4b).



Fig. 3.5 Unilateral ulnar deviation

Most of the times, RA presents with symmetrical involvement of the joints, but there are cases with unilateral involvement of the more affected dominant hand (in this case the right hand). This patient suffers from advanced RA with ulnar deviation of the right hand. Note also the rupture of the extensor tendon of the 5th digit. The left hand is less affected by the RA process.



Fig. 3.6 Hitchhiker's thumb or Z deformity

A hitchhiker's thumb may occur in RA. It can be unilateral or bilateral and it consists of hyperextension of the interphalangeal joint, and fixed flexion and subluxation of the MCP joint. This is a sign at a later RA stage. Note the considerable MCP joint thickening, subluxation and ulnar deviation of the fingers.

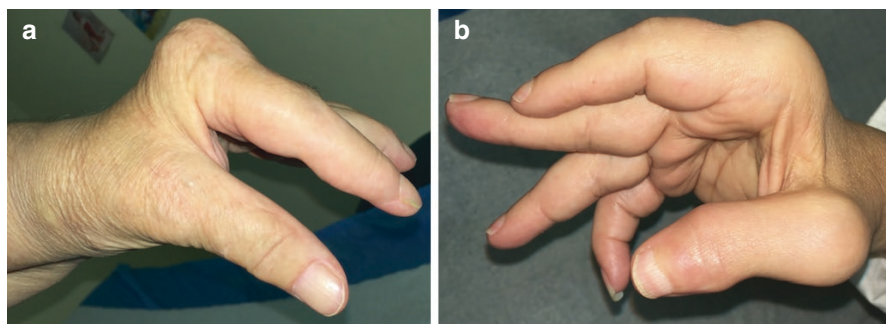


Fig. 3.7 Dysfunctional grip

Volar subluxation of the MCP joints in RA. It may be present in advanced cases of RA. Usually, when there is subluxation of the MCP joints associated with ulnar deviation of the fingers the result is a dysfunctional grip. These patients in Fig. 3.7a and b have difficulties in their everyday life when fine movements of the fingers are needed. Lateral and palmar prehension is also affected.



Fig. 3.8 Boutonniere and swan-neck deformities

Patients with longstanding RA often develop two characteristic finger deformities. In Fig. 3.8a, a patient with boutonniere deformity of the middle finger and in Fig. 3.8b a patient with swan-neck deformity of the 5th finger of the left hand are shown. The boutonniere deformity is the result of hyperextension of distal interphalangeal (DIP) and MCP joints with flexion of PIP joints whereas swan-neck deformity is the result of hyperextension of PIP joint with flexion of DIP joint. In some cases, such as in this in Fig. 3.8c both finger deformities can be present (insert figure in lateral view).



Fig. 3.9 Extensor tendon rupture

Tendon rupture is not an uncommon finding in RA. Usually the ulnar side is most affected, especially the 4th and 5th digits. It can be due to chronic synovitis or erosions of the distal ulna.

All the above patients had established RA and presented with inability to extend their fingers due to extensor tendons rupture of these digits. Black arrows show the affected digits of every patient. Note also the MCP subluxation and the ulnar drift of their fingers.



Fig. 3.10 Caput ulnae syndrome

In caput ulnae syndrome the distal radio-ulnar joint is involved. It is characterised by prominent appearing distal ulna (yellow arrow) and it develops as the supporting ligaments around the distal ulna deteriorate and the extensor carpi ulnaris subluxates anteriorly causing flexion and supination of the carpus.



Fig. 3.11 Tenosynovitis in rheumatoid arthritis

The dorsal extensor tendon sheaths may be affected by synovitis. In Fig. 3.11a a typical swelling of the dorsal tendon sheaths is shown.

In Fig. 3.11b a distal dorsoradial tenosynovitis is shown. This is caused mostly by repetitive wrist flexion and extension or by direct trauma to the second extensor compartment and rarely by RA in sine.

The main complain of patients presenting with these manifestations is pain and limited range of motion (ROM) of the wrist. Crepitus may be evident on palpation.



Fig. 3.12 Synovitis

Synovitis is the hallmark feature of RA. Synovitis may be acute or chronic. In advanced long-standing cases of RA, chronic synovitis of the wrists and finger joints is seen.

In Fig. 3.12a, a typical hourglass-shaped swelling is shown due to dorsal synovitis of the wrist (black arrowheads point towards the hourglass incision).

Figure 3.12b shows a patient with marked synovial swelling of the wrist as well as the MCP joints with subluxation and muscle atrophy.

Figure 3.12c and d show another patient with swelling and subluxation of the MCP joints as well as mild interosseous muscle atrophy.



Fig. 3.13 Rheumatoid nodules

In Fig. 3.13a, a patient with established RA and multiple subcutaneous nodules on both hands, whereas in Fig. 3.13b multiple, firm RN on the extensor surface of the left forearm and elbow in a male patient with seropositive RA are shown. The nodules are usually present on the extensor surfaces of the hands and feet. Usually on palpation they are firm rather than hard or soft. They arise most commonly over pressure points such as the elbows (Fig. 3.13b) or the Achilles tendon but may occur anywhere. The eyes and lungs can also be affected. The presence of RN may occur at any stage of the disease, usually in males, smokers who are seropositive for RF and ACPA. RN seem to correlate with a not-favourable disease progression. In differential diagnosis, chronic tophaceous arthritis should be ruled out. In Fig. 3.13a, the diagnosis of Garrod's pads and olecranon bursitis in Fig. 3.13b should also be ruled out.

Fig. 3.13 (continued)**Fig. 3.14** Different cases of rheumatoid nodules

As discussed in Fig. 3.13, RN can develop in different sites of the skin or even other organs. In Fig. 3.14a–h, some of the most common sites of appearance are presented. In Fig. 3.14i, multiple, firm nodules on the volar aspect of the right forearm are shown. This is a clinical presentation of a male patient with multiple subcutaneous lipomata. Usually, RN appear on the extensor surfaces. Nevertheless, the diagnosis can be made by a detailed history (absence of symptoms and clinical signs suggesting RA), laboratory tests (acute phase reactants within normal limits, RF negative) and histology which confirms the diagnosis. The term rheumatoid nodulosis is used when multiple nodules exist (Fig. 3.14c).



Fig. 3.14 (continued)

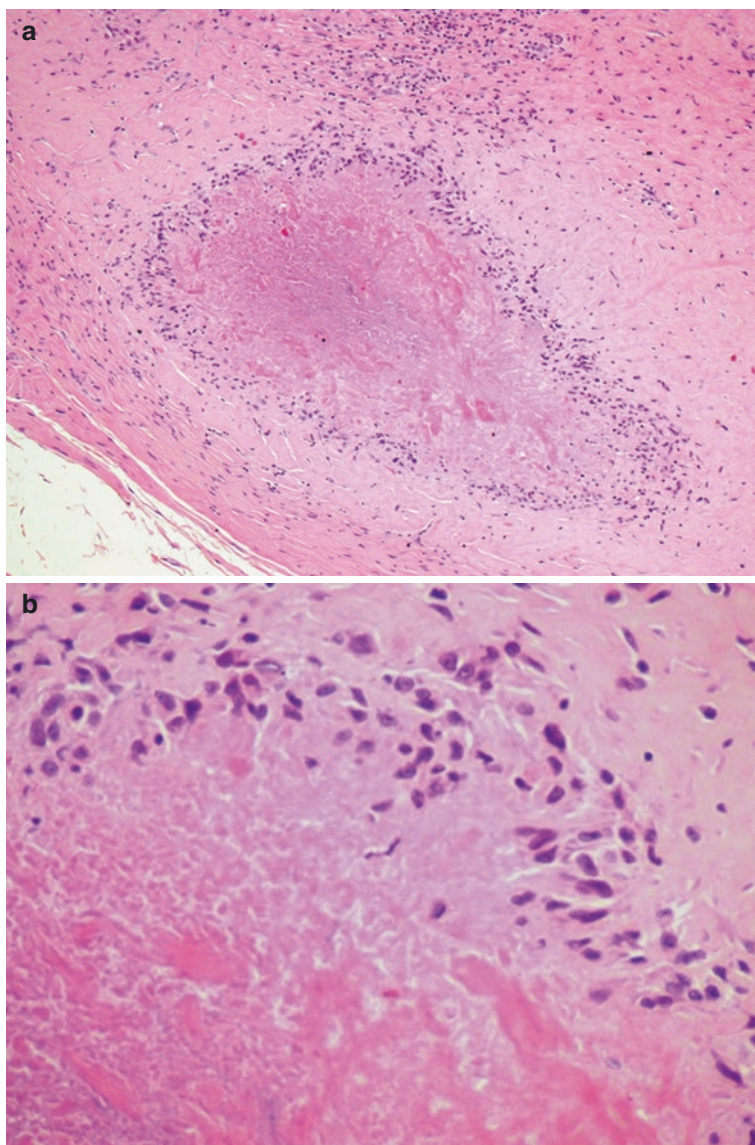


Fig. 3.15 Rheumatoid nodule – histology

Histological examination reveals 3 zones: (a) a central necrotic area mainly composed of fibrin, (b) a surrounding area in which histiocytes and fibroblasts form radiating columns or palisades and c) an outer layer of chronic inflammatory infiltration which contains a variable number of fibroblasts.

In Fig. 3.15a, a RN biopsy, shows a necrotic centre admixed with fibrin surrounded by inflammatory cells, mainly histiocytes, arranged in a palisading fashion (H/E $\times 100$).

Figure 3.15b shows in greater detail the junction of the characteristic zones that make up the typical histological features of the RN shown in Fig. 3.15a. Note the amorphous necrotic zone surrounded by inflammatory cells, mainly histiocytes (H/E $\times 400$).



Fig. 3.16 Joint effusion – acute synovitis

Although RA usually produces a symmetrical small joint arthritis, larger joints are often affected simultaneously. In Fig. 3.16a and b, large effusion of the shoulders is seen and as a result the patient was in pain with marked limited ROM.

In Fig. 3.16c, a bilateral knee effusion is depicted. The MSUS image in d shows the synovial fluid collection (white asterisk) but also the synovial hypertrophy (yellow asterisk).

Figure 3.16e shows the ankle of an RA patient with marked swelling. Again, with the use of MSUS, a semi-quantitative score can be used to estimate the effusion of the ankle joint as seen in Fig. 3.16f on a longitudinal midline anterior view through the tibio-talar joint.

A Baker's cyst or popliteal cyst may be present in patients with knee effusions. Note the well-defined margins as well as the synovial fluid and the synovial hypertrophy within the cyst in Fig. 3.16g and h.



Fig. 3.17 Elbow deformities

This is a seropositive female patient suffering from RA for approximately 30 years. In the above figures a complete destruction of the humeroulnar and humeroradial joints is shown. Nevertheless, this patient was able to flex and extend her elbow with limited ROM. After 15 years, almost 2 of 3 patients with RA present definite involvement of the elbow joint. Note also that there are free bodies in the elbow joint (white arrows on Fig. 3.17b and c. Figure 3.17c in a computed tomography three dimensional - CT3D - reconstruction). The contralateral elbow of the same patient is shown in the insert figure.



Fig. 3.18 Forefoot deformities

Malalignment of the MTP joints is typical at a later stage of RA, with lateral deviation of toes (Fig. 3.18a). Classically, the deviation of the toes decreases from the first toe to the fourth. In other cases, such as this in Fig. 3.18b, cross over toes or hammer toes may develop. In these two cases (Fig. 3.18a, b) hallux valgus is also present.



Fig. 3.19 Rheumatoid vasculitis

Rheumatoid vasculitis (RV) is considered an extra-articular manifestation of RA and usually involves small to medium sized vessels, but large blood vessels can also be affected. It is a serious complication in patients with long-standing RA. Generalised symptoms such as fever and weight loss are common. It can be manifested as digital ischaemia (Fig. 3.19a) or even gangrene of the distal parts of the extremities, cutaneous ulceration that commonly involves the ankles. The most common manifestation is peripheral vascular lesions in the form of localised purpura (Fig. 3.19b–d).

There are no specific laboratory tests for the diagnosis but high levels of acute phase reactants, hypocomplementaemia, and positive ANA are common. Markedly elevated RF levels is another clue in the appropriate clinical context for the correct diagnosis. Deep skin biopsies from the edge of skin lesions are very useful in detecting medium-vessel vasculitis. Depending on the severity of the RV, oral CS can be used. Cyclophosphamide (CP) is usually warranted for severe cases of organ involvement.

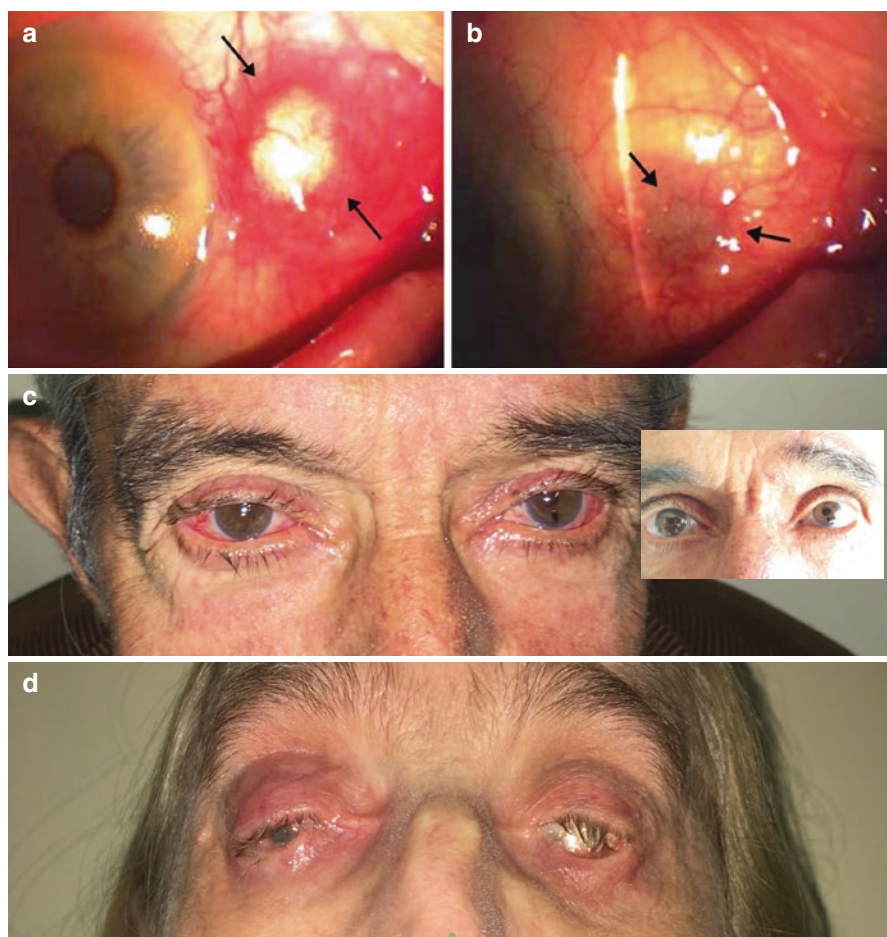


Fig. 3.20 Ocular manifestations in rheumatoid arthritis

Scleritis is a chronic, painful, and potentially blinding inflammatory disease that is characterised by oedema and cellular infiltration of the scleral and the episcleral tissues. The most common clinical forms are nodular and diffuse scleritis. In Fig. 3.20a and b anterior nodular scleritis in a woman with RA is presented. Figure 3.20a shows the acute phase (black arrows showing the nodular lesion). Figure 3.20b shows the phase of regression with thinning of the sclera (black arrows). In Fig. 3.20c, a 71-years old male with diffuse scleritis is shown. The insert figure shows the same patient after treatment. This ocular complication requires urgent treatment with immunosuppressive medications because if left untreated blindness can occur.

In Fig. 3.20d, a female patient with RA and scleritis in the past that led her to blindness.

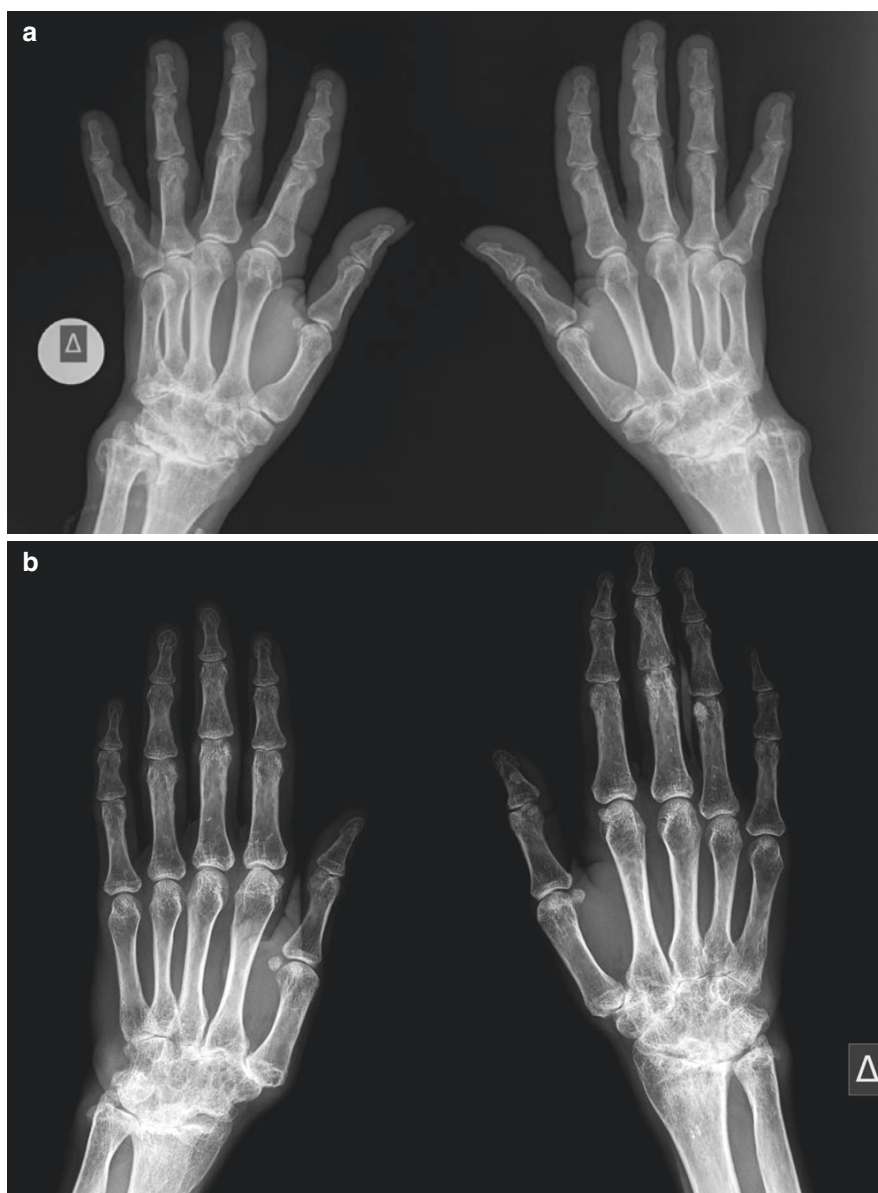


Fig. 3.21 Hand x-rays

Early x-ray findings include the development of periarticular osteopenia. The characteristic bony changes include marginal erosions, subchondral cyst formation, juxta-articular osteopenia, subluxation and dislocation as well as ankylosis in severe cases. The distribution of the affected joints of the hand include the carpal bones, the MCP joints and PIP joints. Posteroanterior (PA) conventional radiograph of the hands in a 55-years old patient with longstanding RA. Severe erosive changes of the carpal bones on both hands with joint space narrowing of the MCP and PIP joints. Multiple subchondral cysts are also evident (Fig. 3.21a). In Fig. 3.21b, the most prominent finding is the fusion of the carpal bones with totally deranged anatomy. Periarticular osteopenia is also evident.

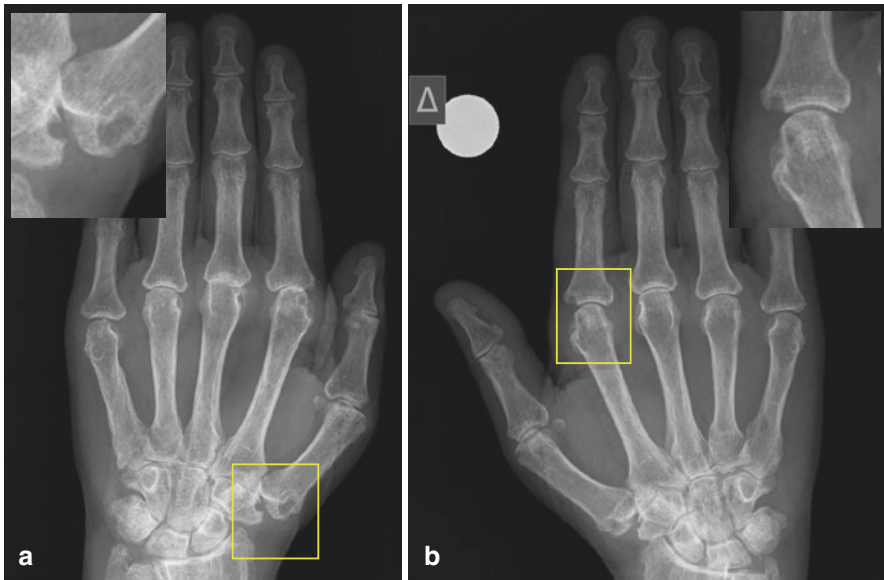


Fig. 3.22 Large bone erosions and cyst formation

Conventional radiography of the hands depicting large cyst formation and joint space narrowing of the carpal bones. Note also large erosive changes of the trapezium on the left hand and a large cyst on the carpometacarpal joint (Fig. 3.22a yellow rectangle – insert figure in magnification). At the MCP's level note marginal erosions on the 2nd – 4th MCP joints and joint space narrowing. Finally, a large erosive lesion is shown in the 2nd MCP joint of the right hand (Fig. 3.22b yellow rectangle – insert figure in magnification).

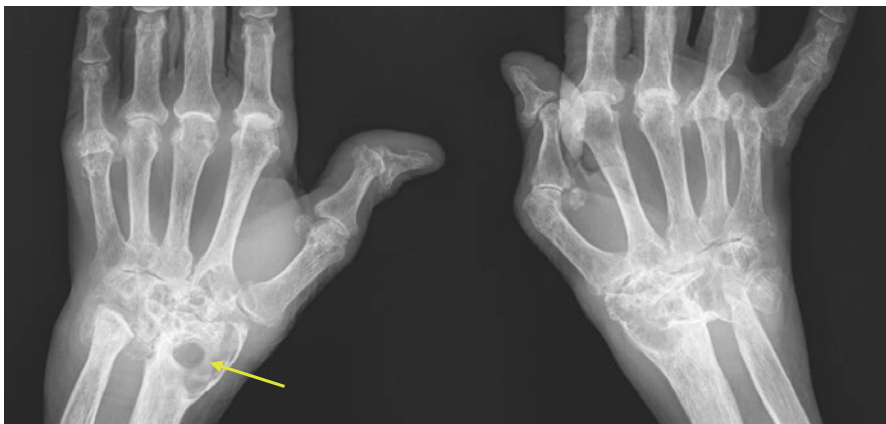


Fig. 3.23 Bone cyst mimicking Brodie's abscess

Sometimes bone cysts in patients suffering from RA may become large enough to produce an image like the one on the radial head of the left hand (yellow arrow) mimicking Brodie's abscess (subacute osteomyelitis). Marginal erosions are also evident. Note also the subluxation of the 5th MCP of the right hand, as well as severe erosions with joint space narrowing of all MCP joints bilaterally. Severe destructive changes are also shown in the carpal bones.

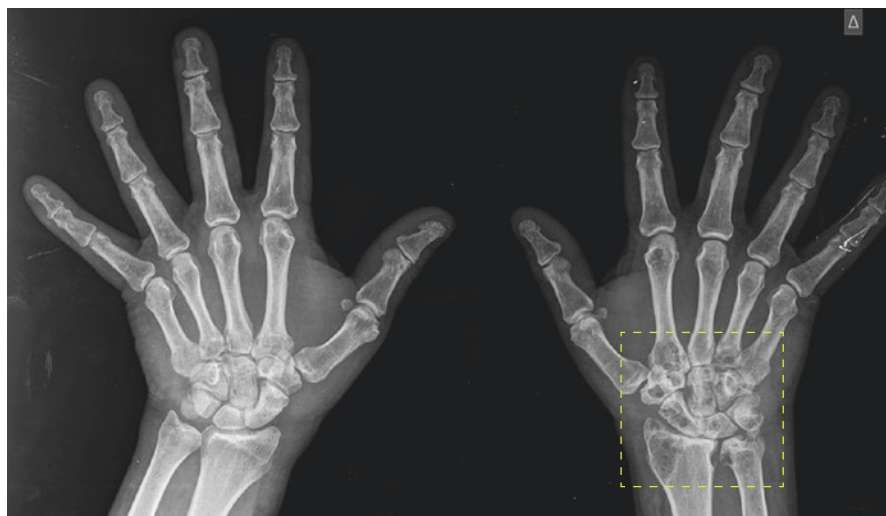


Fig. 3.24 Multiple bone cysts

Following the previous figures, bone cysts in RA may have a variety of manifestations in hand plain radiography. Most of the times, the dominant hand (right-handed patient in this instance) presents more severe pathology in comparison with the contralateral. This is a 60-years old male patient working as a builder. You can notice the extensive bone cyst formation of the carpal bones but also multiple pericarpal cysts on the right hand (yellow dashed rectangle).

Fig. 3.25 Distal radioulnar dissociation

The distal radioulnar joint is involved in approx. 30% of patients with early RA and in approx. 75% in late presentations. The palmar and dorsal radioulnar but also other supportive ligaments are affected. The radioulnar joint is often the first compartment of the wrist involved in patients with RA. Distal radioulnar dissociation (white arrow) can be the result of trauma but also osteoarthritis (OA). Note the bone cysts that are also present (black arrows) and a bone erosion at the proximal end of the 5th metacarpal bone (black arrowhead).



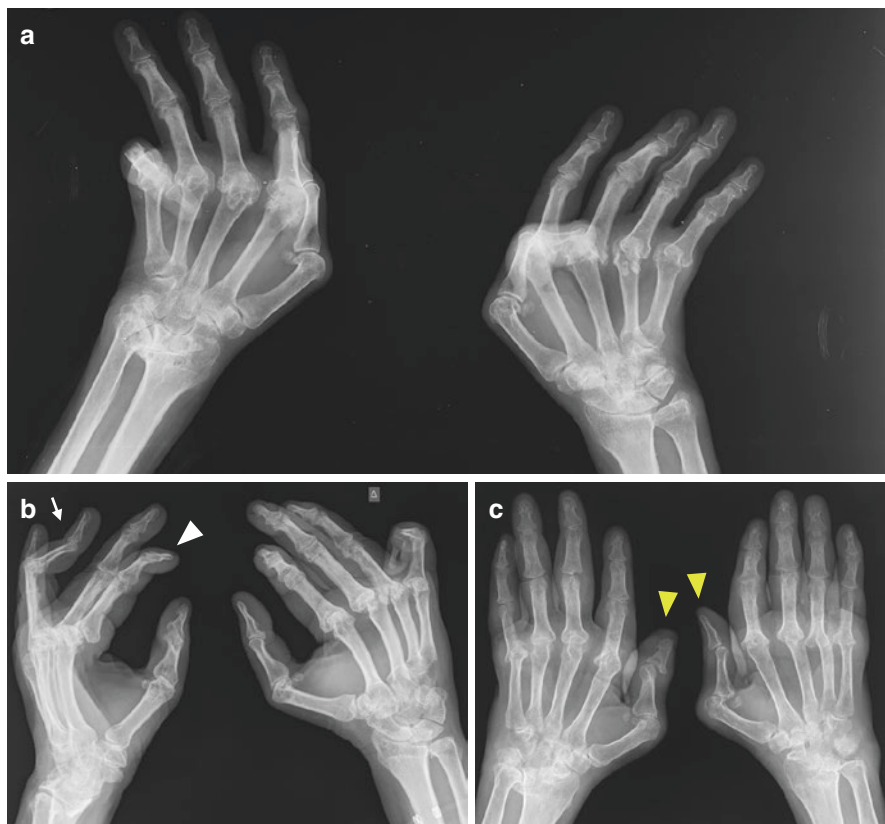


Fig. 3.26 Various hand deformities on plain radiography

Figure 3.26a ulnar drift with anatomic derangement of the carpal bones.

For the clinical picture of ulnar drift see also Fig. 3.4.

Figure 3.26b boutonniere deformity of the 4th finger of the left hand (white arrow), swan-neck deformity of the 2nd finger of the left hand (white arrowhead). Bone cysts are also evident. *For the clinical picture of boutonniere and swan-neck deformities see also Fig. 3.8.*

Figure 3.26c hitchhiker's thumb bilaterally which consists of hyperextension of the interphalangeal joint, and fixed flexion and subluxation of the MCP joint (yellow arrowheads). Anatomic derangement of the carpal bones. Bone erosions of the MCPs. Note also the soft tissue swelling which is seen better on the 2nd and 4th fingers of the left hand.

For the clinical picture of the hitchhiker's thumb see also Fig. 3.6.

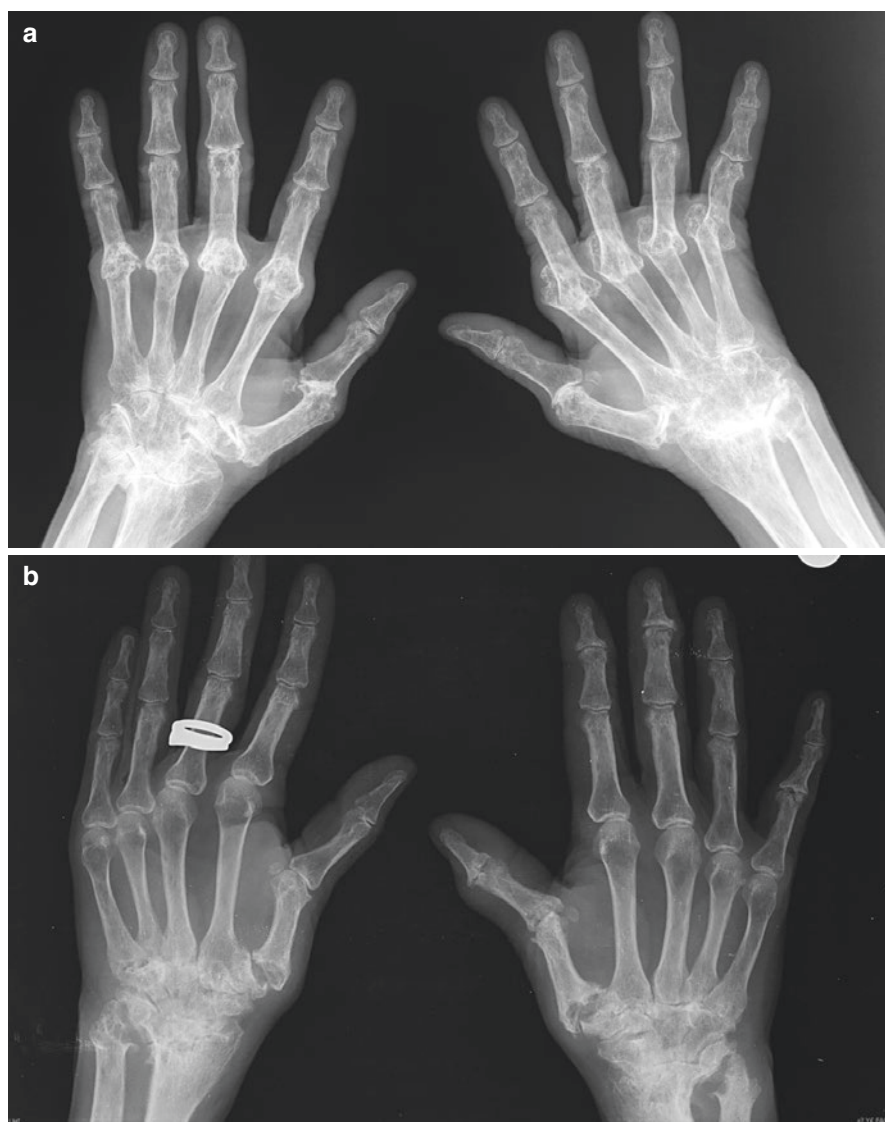


Fig. 3.27 Catastrophic lesions

In Fig. 3.27a, the carpal bones are fused and ankylosed with restricted ROM to all directions of the hands. In addition, subluxation of the MCPs is evident while severe erosive changes are seen in all MCP joints of the right hand. Note also the severe erosions affecting all MCP's and PIP's in both hands. In Fig. 3.27b a 52-years old male smoker with seropositive RA and disease duration of approximately 18 years is presented. Hand and wrist radiographs show severe and extensive erosive changes involving the ulna, radius and the carpal bones which are fused. Large erosions are also evident in the carpometacarpal (CMC) joints as well as in the first MCP's bilaterally. Finally, joint space narrowing is seen involving all PIP's and MCP's bilaterally.

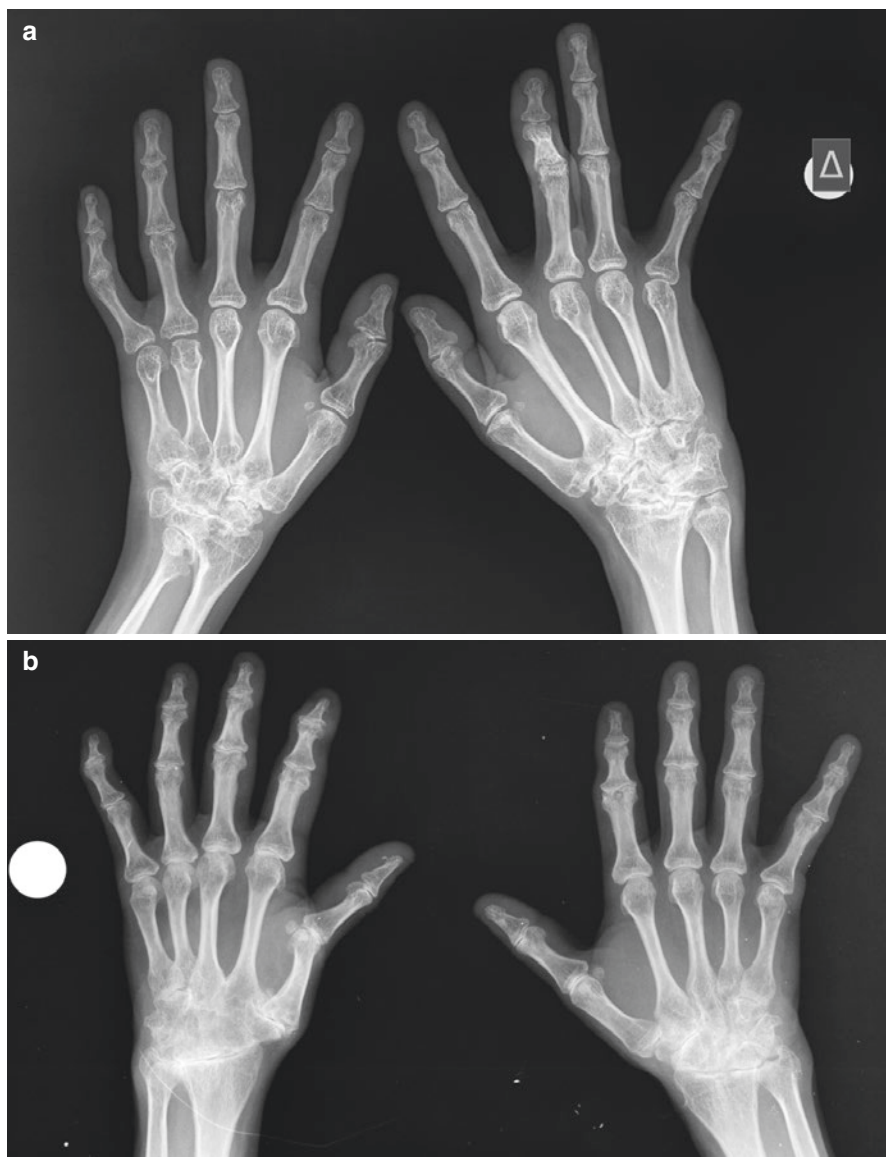
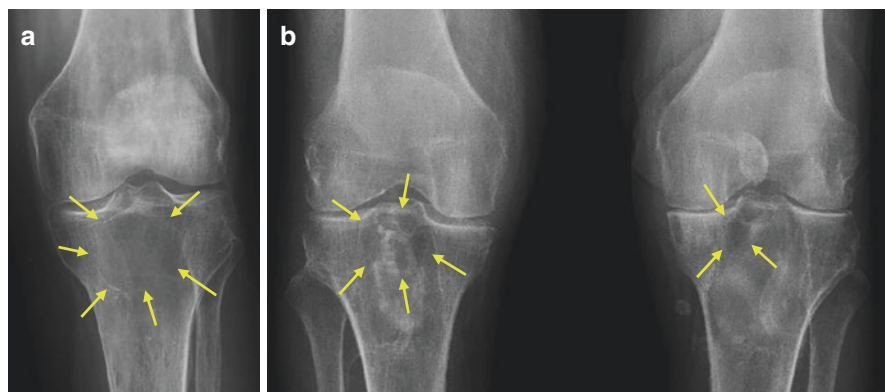


Fig. 3.28 Juvenile idiopathic arthritis – hands

In Fig. 3.28a, a 30-years old male with idiopathic juvenile arthritis with symmetric involvement of the carpal bones with erosive changes, joint space narrowing affecting all carpal bones. Subluxation of the 5th finger (right hand). Note also the 4th and 5th metacarpals of the left hand that appear shorter in comparison with the ones of the right hand. In Fig. 3.28b, a 45-years old female suffering from juvenile idiopathic arthritis. Note the periarticular osteopenia which is more prominent in all MCPs. The carpal bones are fused which do not permit any movements on both wrists. Note also diffuse osteopenia involving mainly the carpal bones.

Fig. 3.29 Shoulder

This is a not so common case of shoulder involvement in an RA patient. This is a conventional radiograph of the right shoulder in which severe joint space narrowing of the glenohumeral joint is shown as well as subchondral sclerosis along the glenoid surface and new bone formation in a 60-years old patient with advanced RA.

**Fig. 3.30** Geode in rheumatoid arthritis

Geodes are well-defined lytic lesions on plain radiographs and they can be described as subchondral cysts. It is not a specific finding of RA patients. Geodes are seen in a variety of disorders apart from RA including degenerative joint disease, calcium pyrophosphate dihydrate disease (CPPD), avascular necrosis. In Fig. 3.30a, a 36-years old female suffering from PA is presented with a large geode of the left knee. Figure 3.30b, shows a 78-years old female suffering from seronegative RA with multiple geodes on both knees. The yellow arrows demarcate the limits of the geodes.

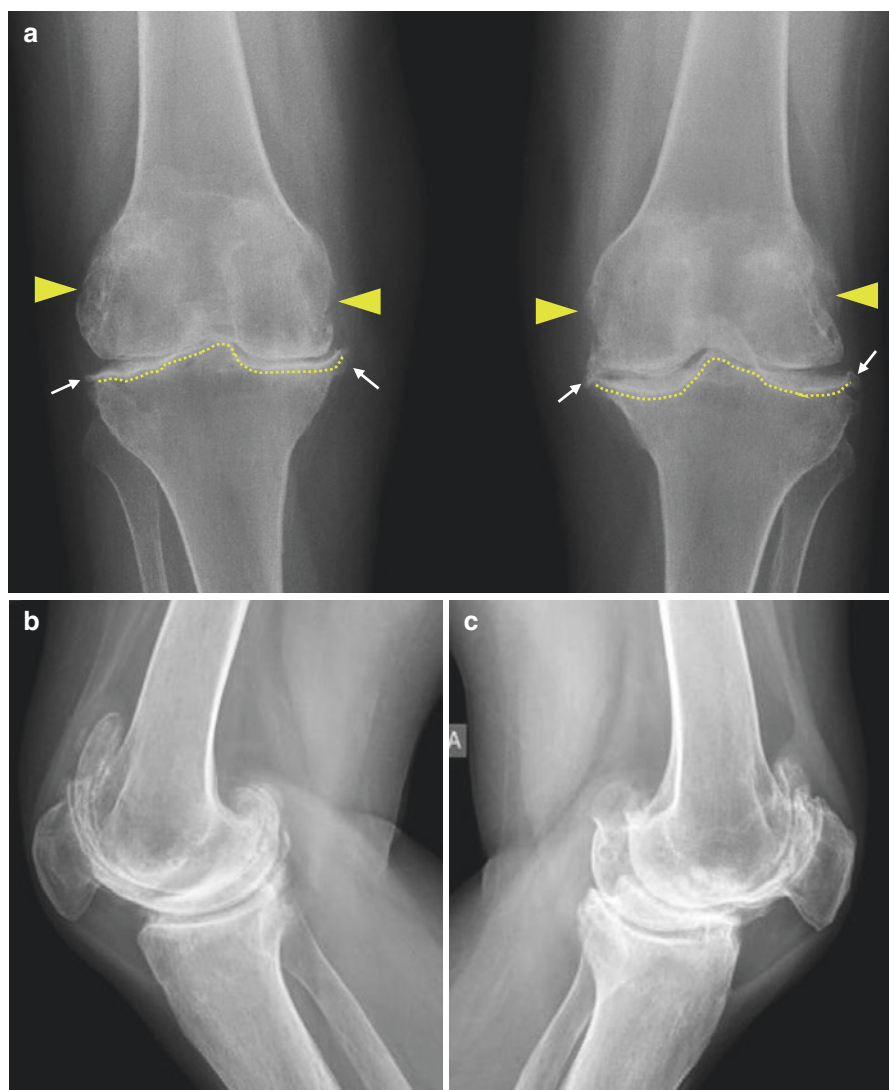


Fig. 3.31 Knee involvement

Conventional radiography of the knees in a patient with longstanding RA. Note the erosive changes affecting the femoral condyles (yellow arrowheads). In Fig. 3.31a there is marked subchondral sclerosis (yellow dotted lines) with cyst formation on both knees, space narrowing and hypertrophic changes (white arrows) which are more evident in the lateral view radiographs (Fig. 3.31b, c). These findings represent radiographic features of secondary OA.



Fig. 3.32 Foot

The foot and ankle are implicated in more than 70% of patients diagnosed with RA. Metatarsalgia is a common complaint of those patients and it is caused by joint swelling and inflammation. In Fig. 3.32a, the patient has longstanding RA and the main feature of this radiograph is the symmetrical subluxation of the MTPs (white arrows). Marginal erosions are also evident with multiple cysts formation (white arrowheads). Hallux valgus is present in the first MTPs (white dashed lines). In RA patients, chronic inflammation could also lead to arthritis of the transverse tarsal joint (Chopart joint), especially after local trauma as seen in this patient (black dotted line). Another patient with similar findings is depicted in Fig. 3.32b. The most striking findings are the erosions and the bone cysts (white dashed rectangles).



Fig. 3.33 Cervical spine involvement

Loss of the normal curvature of the cervical spine (yellow dashed line: normal) with subaxial subluxation at the level of C5,6,7. Note also the joint space narrowing of the vertebral articular facets at the level of C3 – C4 (yellow arrow).

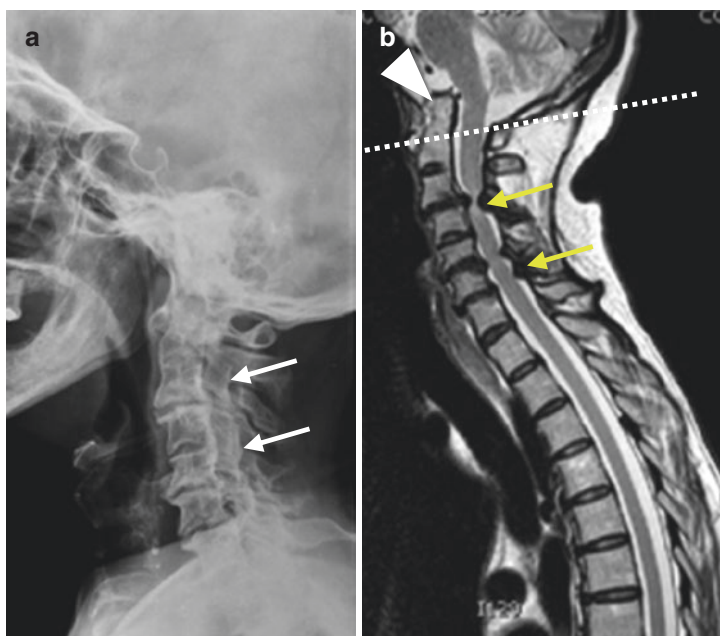


Fig. 3.35 Lung involvement

Pulmonary symptoms occur months or years after the onset of the joint disease. Clinical signs may include dyspnoea, cough, and recurrent infections but may be asymptomatic. High resolution CT is more sensitive than pulmonary function tests. The patterns of interstitial disease are diverse and include nonspecific interstitial pneumonia (NSIP), UIP, cryptogenic organising pneumonia and follicular bronchiolitis. The most common pattern being UIP.

In Fig. 3.35a, a male patient with seropositive RA. There is an RN on the right lung base with mild thickening of the surrounding interlobular septae.

Figure 3.35b, shows a female seropositive RA patient with pulmonary fibrosis on both lung bases, honeycombing, ground-glass opacities and interlobular septae thickening.

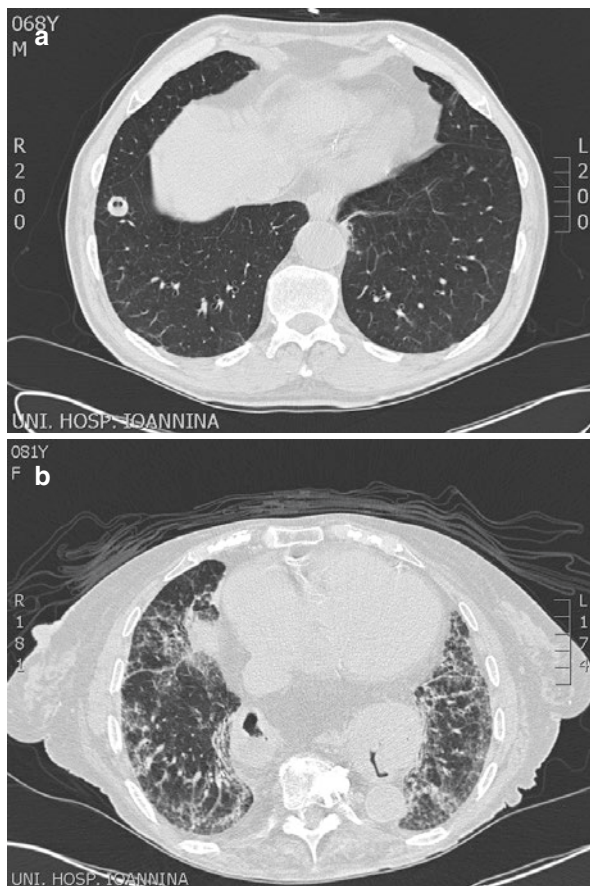


Fig. 3.34 Cervical spine involvement – a severe case

A female patient with long-standing RA who never achieved remission. Note the extensive degenerative changes of the vertebral bodies but also the fusion of the spinous processes C2-C3 and C4-C5 (Fig. 3.34a – white arrows). In Fig. 3.34b, an MRI scan of the same patient showing compression of the spinal cord at multiple sites (yellow arrows). Basilar invagination (BI) is also visible (white arrowhead). BI is due to loss of axial supporting structures in the upper cervical spine. If the dens is more than 3 mm above the Chamberlain's line (white dotted line), the patient has basilar invagination and is at risk of multiple pathologies and even death.

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Chapter 4

Sjögren's Syndrome



4.1 Introduction

Sjögren's syndrome (SS) is a chronic, slowly progressive autoimmune exocrinopathy characterised by mixed cellular infiltration of exocrine glands, notably the lacrimal glands and salivary glands. Xerostomia and xerophthalmia are prominent features of SS, but every epithelial surface can be affected such as nose, throat and vagina. The term *autoimmune epitheliitis* has been suggested recently. The combination of dry eyes and dry mouth is often referred to as *sicca syndrome*. SS can be primary or secondary. Secondary SS can be seen in patients with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma (SCL) etc. The first description of SS is credited to the Polish surgeon Johann von Mickulicz who, in 1892, described a 42-year-old man with enlargement of the parotid and lacrimal glands associated with a round-cell infiltrate and acinar atrophy. In 1930, Henrik Sjögren coined the term *keratoconjunctivitis sicca* (KCS) clarifying that this type of xerophthalmia had no relation to vitamin A deficiency. In literature, SS replaced the term keratoconjunctivitis sicca as a more general term.

4.2 Epidemiology

SS represents one of the most common systemic autoimmune diseases, with the wider male to female ratio (1:10). Incidence and prevalence of primary SS varies in different geographical areas. Incidence in Asia, Europe and the United States is 6.5 per 100.000 population, 4.5 and 3.9 respectively. Mean prevalence is 60 cases per 100.000 population.

Risk factors for reduced salivary gland function are different classes of medication (anticholinergics, neuroleptics, diuretics, antihistamines), viral infections, malignancy, diabetes mellitus, dyslipidaemias, prior radiation therapy to the head and neck or trauma and the presence of sarcoidosis.

4.3 Aetiopathogenesis

The exact aetiopathogenesis is unclear but both genetic and non-genetic factors are involved in disease susceptibility and initiation of disease process. The main characteristic is that of a dysregulation of the epithelial cells through an autoimmune response which leads to disease progression. The major histocompatibility complex (MHC) has been implicated in SS. There is also growing evidence of a significant role of the interferon type I (IFN) system in determining the disease process. The

presence of IFNs, potent antiviral proteins, reinforce the notion of the role of viral infection in SS pathogenesis. Cytokines network, produced by epithelial cells, contributes to lymphocytic infiltration in the affected tissue consisting mainly with CD4⁺ T cells, B cells, plasmacytoid dendritic cells and macrophages leading to tissue damage.

4.4 Classification Criteria

Since 1993, a number of classification criteria sets for SS have been proposed by single experts or groups of multidisciplinary specialists. In 2016, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for primary SS have emerged. These final classification criteria are based on the weighted sum of five items: anti-Ro (SSA) antibody positivity and focal lymphocytic sialadenitis with a focus score of ≥ 1 foci/4mm², each scoring 3; an abnormal Ocular Staining Score of ≥ 5 (or van Bijsterveld score of ≥ 4), a Schirmer's 1 test result of ≤ 5 mm/5 min and an unstimulated salivary flow rate of ≤ 0.1 mL/min, each scoring 1. Individuals with signs and/or symptoms suggestive of SS who have a total score of ≥ 4 for the above items meet the criteria for primary SS. Sensitivity and specificity is 96% and 95% respectively.

4.5 Signs and Symptoms

SS usually runs an indolent course. Initial manifestations may be mild, and years may elapse from the initial manifestations to the full-blown development and recognition of the syndrome.

Glandular manifestations: lacrimal gland involvement with diminished tear production leads to KCS. Patients usually complain of a burning, sandy, or scratchy sensation and there may be a mild photophobia. Salivary gland involvement leads to xerostomia due to decreased production of saliva. The main symptoms include difficulty in swallowing dry food, inability to speak continuously, changes in sense of taste, and a burning sensation in the mouth. Later on, they can end up with severe dental caries. Parotid or major salivary gland enlargement occurs in about 60% of primary SS patients. The parotid gland enlargement may be unilateral or bilateral. Bronchitis and pneumonitis due to dryness of the upper respiratory tract can occur but also loss of vaginal secretions or pancreatic dysfunction.

Extraglandular manifestations: approximately 20–25% of patients will develop systemic manifestations. Extraglandular manifestations are divided in

periepithelial (arthritis, interstitial nephritis, liver involvement, obstructive bronchiolitis) and extraepithelial manifestations (palpable purpura, glomerulonephritis, and peripheral neuropathy). The former appear early in the disease and usually have a benign course. In contrast, the latter appear late in the disease and are associated with increased morbidity and risk for the development of lymphoma.

Respiratory tract manifestations: a non-productive cough secondary to dryness of tracheobronchial mucosa or dyspnoea due to small airway obstruction is relatively common. Interstitial lung disease is less common. Other findings are pleural effusions and lung nodules or hilar/mediastinal lymphadenopathy which should always alert the physician for the possibility of lymphoma.

Musculoskeletal manifestations: arthralgias and myalgias may be present in up to 70% of patients. A rheumatoid-like non-erosive, non-deforming polyarthritis is occasionally the case. Inflammatory myositis has been also reported.

Gastrointestinal manifestations: dysphagia is very common and it could be due to dryness of the pharynx and esophagus or due to abnormal esophageal motility. Subclinical pancreatic involvement with increased levels of amylase can be seen in about ¼ of SS patients. In case of *helicobacter pylori* infection, eradication treatment should be applied because of its association with gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

Raynaud's phenomenon (RP): approximately 30% of SS patients present with RP before sicca manifestations.

Renal manifestations: interstitial nephritis or glomerulonephritis may develop in 5% of primary SS. Distal renal tubular acidosis may be clinically silent, but if left untreated, nephrocalcinosis and compromised renal function may develop.

Neurologic manifestations: sensorimotor glove and stocking symmetrical neuropathy is observed in approximately 10% of SS patients. Dementia and multiple sclerosis like symptoms may appear from the central nervous system.

Blood manifestations: there is a 44-fold greater risk of lymphoma development. The earliest manifestation may be a monoclonal gammopathy.

4.6 Diagnosis and Differential Diagnosis

The diagnosis of SS is usually a clinical one based on the history, physical examination with support from the laboratory findings and applying also the diagnostic criteria. The differential diagnosis includes disorders and conditions causing dry eyes and parotid gland enlargement. Thus, a careful past medical history to exclude recent or past viral infections, diabetes mellitus, dyslipidaemia, prior radiation, trauma, the presence of sarcoidosis and the intake of drugs (diuretics, antihistamines, anticholinergics, neuroleptics) is an imperative.

Imaging: plain radiography and High-resolution Computed Tomography (HRCT) are the most used imaging techniques not for the diagnosis of SS but for observation

of the respiratory tract manifestations (interstitial lung disease, pleural effusions, lung nodules, lymphadenopathy).

Lip biopsy: examination of the minor salivary glands is the most common invasive diagnostic procedure for SS. The findings are consistent with lymphocytic infiltration of the minor salivary glands.

Schirmer's test: special filter paper strip used to measure tearing. If after 5 minutes wetting of the paper is less than 5 mm, then the test is considered positive. The test can be performed with anaesthetic (Schirmer 1) or without anaesthetic (Schirmer 2). Theoretically, a Schirmer 1 evaluates baseline secretion whereas a Schirmer 2 (without anaesthetic) measures baseline plus reflex secretion.

Rose Bengal staining: in SS, slit lamp examination after rose Bengal staining shows a punctate pattern of filamentary keratitis.

Tear break-up time: a drop of fluorescein is instilled into the eye, and the time between the last blink and appearance of dark, non-fluorescent areas in the tear film is measured. A rapid break-up is considered positive.

Laboratory:

Full blood count (FBC) with differential is essential in patients with SS due to the fact that some patients may develop leukopenia, anaemia of chronic disease or thrombocytopenia. Immunological tests are essential for the diagnosis.

Antinuclear antigens (ANA) can be found positive in more than 80% of patients with positive Ro (SSA) and La (SSB) extractable nuclear antigens (ENA). *Ro (SSA)* and *La (SSB)* should be assessed in all patients considered for SS.

Complement levels also are useful. Usually, C3 and C4 levels are within normal limits, but, in case of systemic manifestations or development of lymphoma, there is a decrease of C4 or C3 levels.

4.7 Management

SS management is primarily symptomatic. Xerostomia is difficult to treat. Pilocarpine, a muscarinic agonist, is used to stimulate the salivary flow. Oral hygiene is imperative to prevent dental disease.

Xerophthalmia can be treated with artificial tear drops and ocular ointments.

Hydroxychloroquine (HCQ) can be effective in a subgroup of patients with arthralgias.

Corticosteroids (CS) reduce inflammation and may slow joint damage.

Severe extraepithelial disease requires high-dose systemic CS therapy and an immunosuppressive agent, such as methotrexate (MTX), cyclophosphamide (CP) or rituximab (RTX).

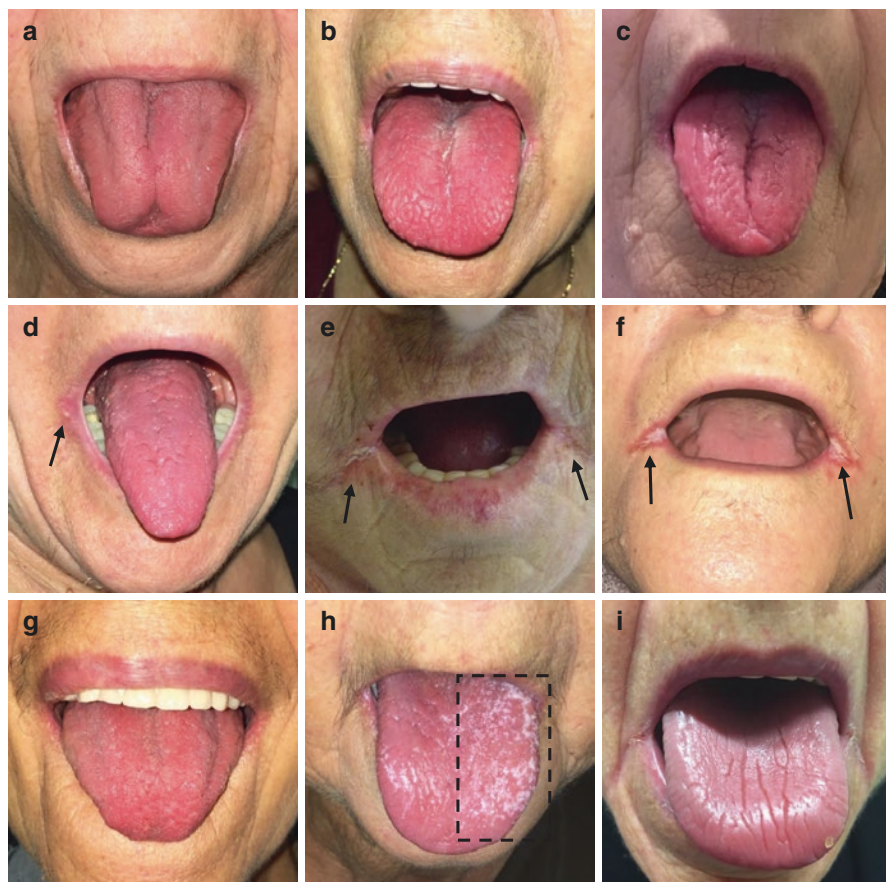


Fig. 4.1 Xerostomia in Sjögren's syndrome

The term xerostomia comes from the Greek word *xeros* (dry) and *stoma* (mouth), which means dry mouth. Xerostomia has a variety of possible causes. SS is the most common autoimmune disease characterised by inflammation of the exocrine glands and may occur independently (primary) or in association with other autoimmune diseases such as RA, SLE, or SCL (secondary SS). Xerostomia can lead to poor quality of life. Some symptoms/complications of this disorder are: thirst, difficulties in oral function, dysphagia, taste disturbances, altered speech, mucosal changes, injuries of oral mucosa, oropharyngeal burning, food retention in the mouth, plaque accumulation, fungal infections.

In this figure patients with primary SS and dry mouth with various dryness complications are presented. In Fig. 4.1a–c dry mouth and glossitis in various forms are shown. In Fig. 4.1d–f different types of angular cheilitis from mild to severe cases are depicted (black arrows). Figure 4.1g shows a patient with xerostomia and false denture due to severe tooth erosions in the past. In Fig. 4.1h a patient with dry mouth and oral candidiasis (white spots more evident in the black rectangle) is shown. Finally, in Fig. 4.1i, a patient with severe xerostomia and tongue fissuring is depicted.



Fig. 4.2 Parotid gland hypertrophy in Sjögren's syndrome

Parotid gland hypertrophy/enlargement is one of the hallmark findings in SS. A very minute clinical examination and a histological examination must differentiate other causes of parotid gland hypertrophy, especially if unilateral (parotid tumour, sarcoidosis, lymphoma etc). Figure 4.2a–c show patients with mild to moderate parotid gland hypertrophy. Figure 4.2d resembles a Warthin's tumour but, histological findings were compatible with SS (lymphocytic infiltrates). Figure 4.2e, f are from the same patient. This patient had sicca symptoms and a severe bilateral parotid gland enlargement resembling parotid tumour.

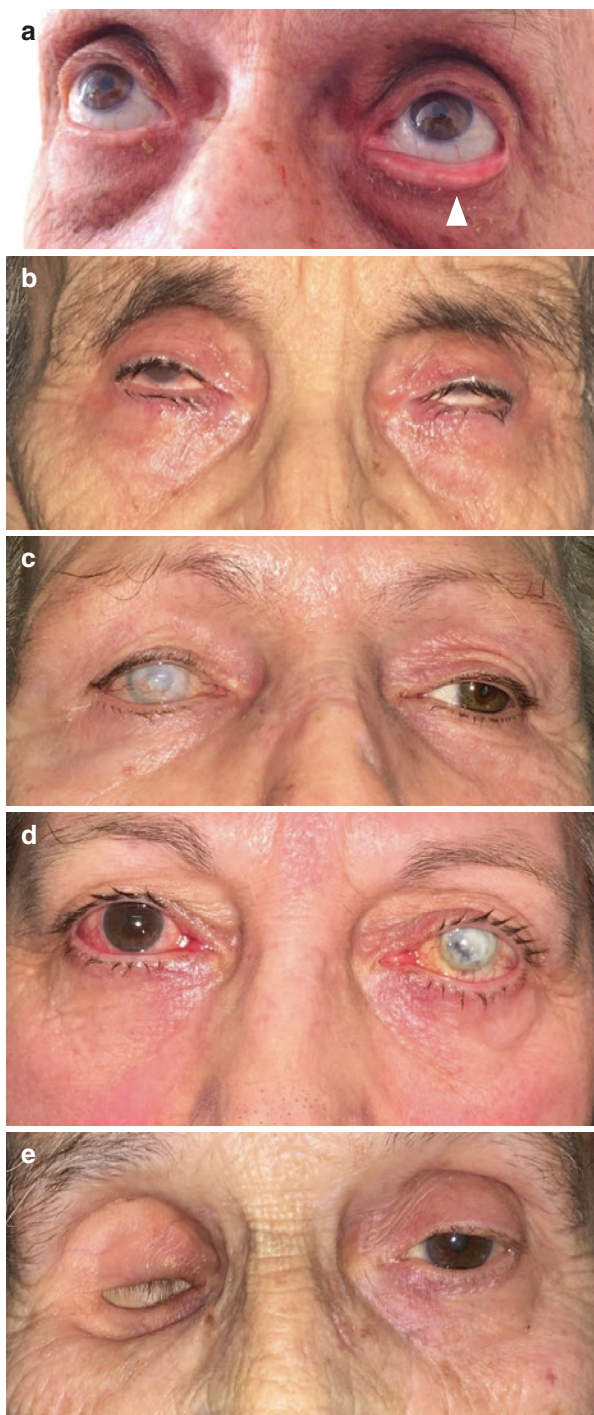


Fig. 4.4 Eye complications in primary Sjögren's syndrome
Peripheral ulcerative keratitis (PUK) with perforated ulcer (black arrow) in a patient with primary SS. This is a severe complication of SS with poor outcomes of the affected eye.

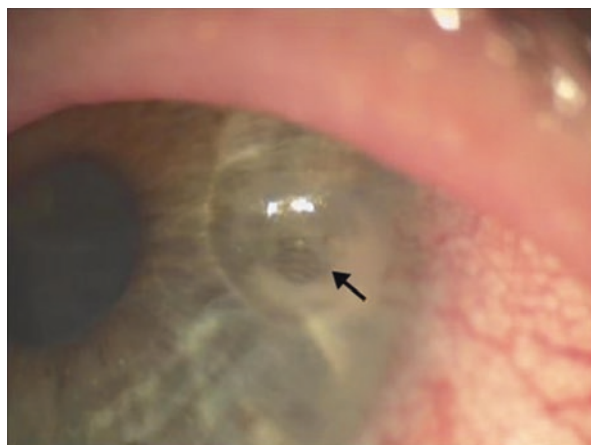


Fig. 4.5 Eye complications in secondary Sjögren's syndrome
Secondary SS with a woman with RA. PUK with perforated cornea and iris prolapsed (black arrow). Note also the reactive hypopyon in the anterior chamber (black arrowhead). Another severe eye complication with poor prognosis in patients with SS.

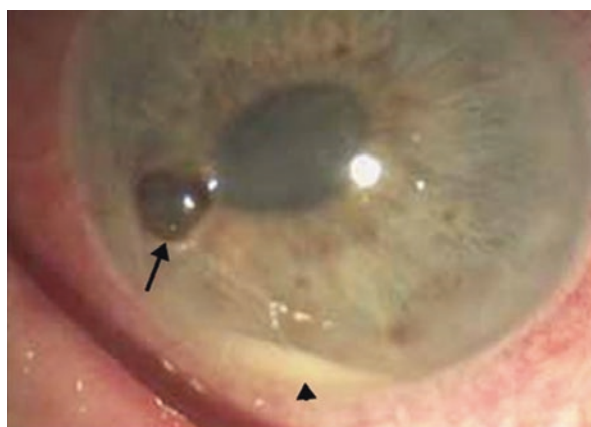


Fig. 4.3 Ocular manifestations in Sjögren's syndrome

Ophthalmologic manifestations of SS may be mild to severe. In some cases, the complications may lead to severe loss of the visual acuity or even to blindness. Severe ocular dryness can cause corneal scarring, ulceration, infection, end even perforation. Dry eyes may be the result of other pathologies such as in the patient in Fig. 4.3a with ectropion of the left eyelid (white arrowhead). Signs and symptoms or even subjective complaints of ocular irritation may be the following: burning, stinging, itching, foreign body sensation, lid irritation and swelling, photophobia, ocular fatigue and mucoid discharge.

There is a variety of tests that can be applied in order to help in the diagnosis of xerophthalmia such as reduced tear break-up time, Schirmer 1 test, rose Bengal staining, lissamine green B.

In Fig. 4.3b a patient with severe photophobia is presented. Note the periocular erythema and mild blepharitis on both eyes.

Figure 4.3c and d show two different patients with SS and corneal scarring. Patient in Fig. 4.3d has also anterior scleritis of the right eye.

In Fig. 4.3e, a patient with refractory to treatment anterior scleritis of the right eye and recurrent infections undergone evisceration of the right eye.



Fig. 4.6 Musculoskeletal involvement in Sjögren's syndrome

Musculoskeletal involvement in SS is typically non-erosive and non-deforming. Arthralgias occur in about half of the patients with SS. Arthritis can be present in 1/3 patients and has a similar distribution to RA but is not erosive. Because of the fact that SS appears in women after the age of 50, clinicians must be aware of differentiating the disease with osteoarthritis (OA) or other findings that are not directly related with the disease. Figure 4.6a and b, show two different patients with primary SS and osteoarthritic changes of both hands.



Fig. 4.7 Hair loss in primary Sjögren's syndrome

Hair disorders are frequently observed in various systemic diseases, including autoimmune connective tissue diseases (CTDs), with predilection of SLE, followed by dermatomyositis (DM) and SCL.

Hair loss has been reported in several other CTDs, including mixed and undifferentiated CTDs, and primary SS, although it is likely to be underestimated in such diseases. In this figure a patient with hair loss suffering from primary SS is depicted.

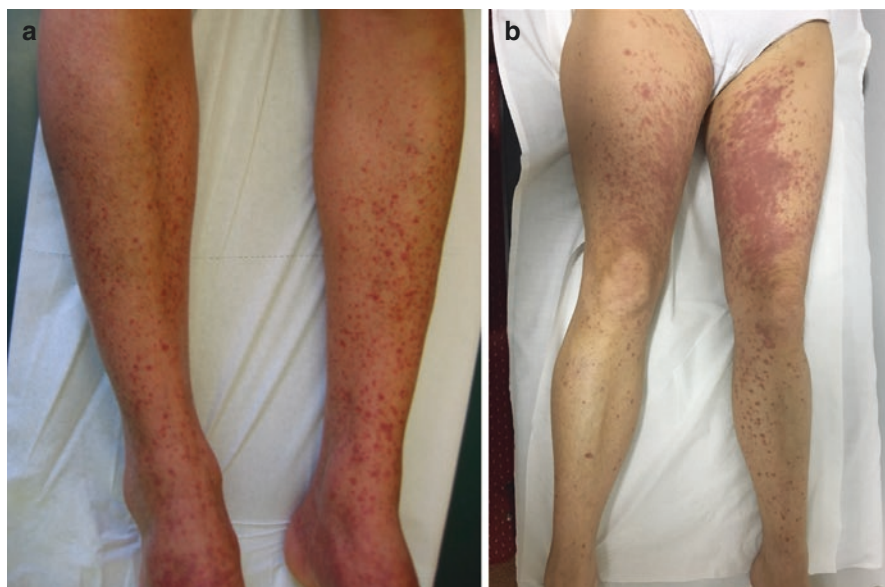


Fig. 4.8 Vasculitis in Sjögren's syndrome

Vasculitis in SS is a prognostic factor for an adverse outcome. Cutaneous vasculitis is the most common form of vasculitis. It can be presented with palpable purpura, urticarial lesions, or erythematous maculopapules. Histological findings reveal a small-sized vessel leukocytoclastic vasculitis.

The triad of hypocomplementaemia (particularly low C4), palpable purpura, and recurrent salivary gland hypertrophy are considered risk factors for the development of lymphoma. In Fig. 4.8a and b, two different patients with SS purpura affecting the lower extremities are shown.



Fig. 4.9 Lip biopsy (labial gland biopsy)

The proposed classification criteria for SS include labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥ 1 focus/4 mm². The lip biopsy has to be interpreted by a pathologist with special training. The result of the biopsy may reveal other types of glandular inflammation and point to alternative diagnosis, such as sarcoidosis, amyloidosis or lymphoma. In this figure the procedure of a minor salivary gland biopsy is shown.

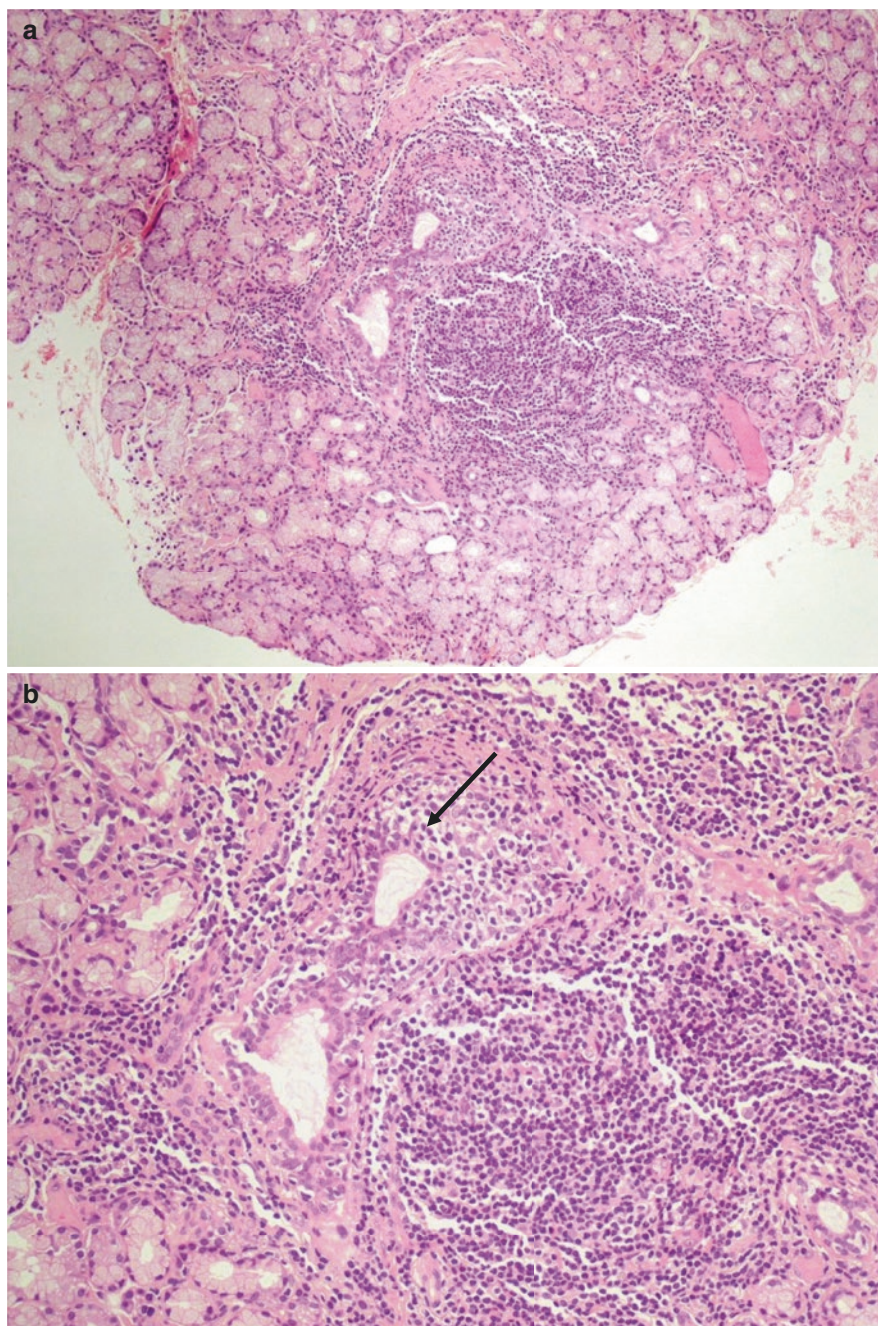


Fig. 4.10 Sjögren's syndrome – histology

A minor salivary gland showing microscopically focal lymphocytic infiltration (at least 50 mononuclear cells) and acinar atrophy (Fig. 4.10a, H/E $\times 100$). Rare epimyoeplithelial islands are present in Fig. 4.10b (black arrow, H/E $\times 200$).

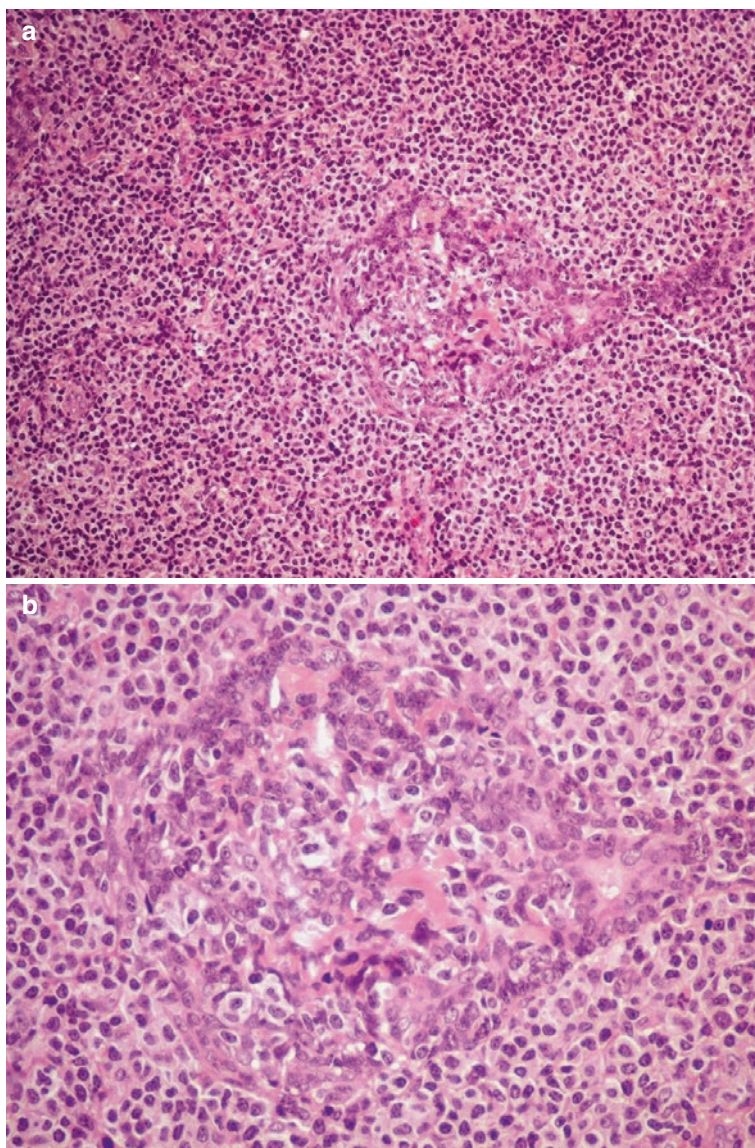


Fig. 4.11 Lymphoma in Sjögren's syndrome

This is an extranodal marginal zone lymphoma of MALT lymphoma.

Figure 4.11a parotid gland biopsy shows dense neoplastic infiltration by medium size lymphocytes (H/E, ×200).

Figure 4.11b the neoplastic lymphocytes infiltrate and destroy epithelial structures of the salivary gland creating the characteristic lymphoepithelial lesions (H/E, ×400).

Figure 4.11c immunohistochemically, the neoplastic population expresses the B-cell marker CD 20 (DAB, ×200).

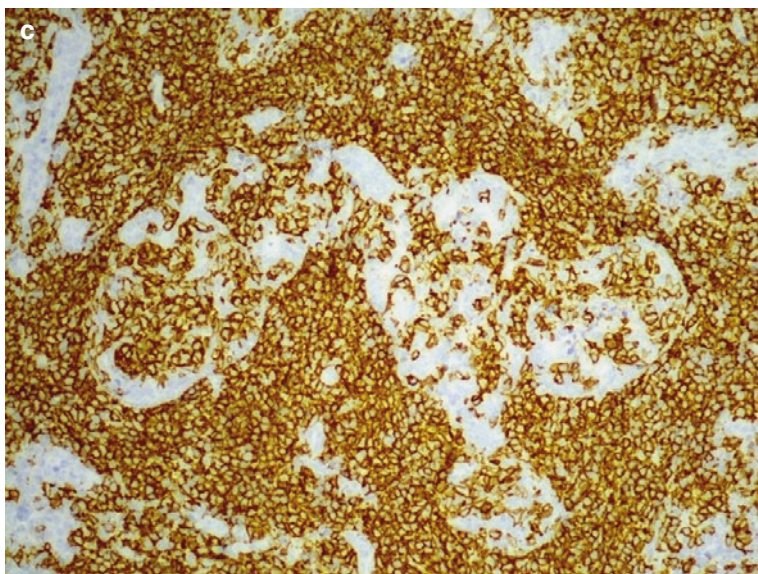


Fig. 4.11 (continued)

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Chapter 5

Psoriatic Arthritis



5.1 Introduction

Psoriatic arthritis (PsA) is a chronic, progressive, seronegative inflammatory arthropathy that often results in permanent joint damage and disability. Skin psoriasis, dactylitis and enthesitis are the hallmarks of the disease. Psoriasis comes from the Greek word “psora” which means “to itch”. The father of medicine, Hippocrates, used tar and arsenic to treat skin psoriasis. It was Galen that identified this particular skin disease and used later the word psoriasis.

5.2 Epidemiology

The prevalence of PsA is common among patients with skin psoriasis but it is low in the general population (1%). On the other hand, until recently, prevalence estimates varied considerably mainly due to different classification criteria used by rheumatologists. Also, because of the great heterogeneity of the disease not only among different continents but also within different regions of the same country, the prevalence ranges between 6% and 41%. There is also growing evidence of cumulative incidence of PsA over time in patients with skin psoriasis.

5.3 Signs and Symptoms

The clinical features of PsA may differ among patients. Monoarthritis or asymmetric oligoarthritis are considered the most common patterns of PsA at initial diagnosis with the skin manifestations to precede the onset of articular manifestations in about 70% of patients. Approximately 15% of patients will develop symptoms of arthritis before skin psoriasis appears. Other clinical patterns of PsA are: symmetric polyarthritis, distal interphalangeal (DIP) arthritis, and destructive arthritis (arthritis mutilans). Pain and synovial swelling of the distal finger and toe joints are common. Patients complain of pain in the second half of the night and/or morning that usually lasts for >30 min. Back pain is a common complaint when the axial skeleton is involved (approximately 20–30% of cases). Often, additional complaints due to enthesitis, bursitis, and dactylitis (sausage digit) are present. Extra-articular manifestations may involve the skin (excluding psoriasis such as keratoderma blenorrhagicum), nails (nail psoriasis), gastrointestinal tract (inflammatory bowel disease), urogenital tract (urethritis), eyes (uveitis), cardiovascular system (endothelial dysfunction and early atherosclerosis), pulmonary system (apical fibrosis).

5.4 Diagnostic Modalities

Several classification criteria have been created since the original Moll and Wright criteria in 1973 for PsA showing the large heterogeneity of the disease. These criteria have been designed in order to create more homogenous populations for

research but they usually are used as diagnostic criteria as well. The Amor criteria, European Spondyloarthropathy Study Group criteria, Vasey and Espinoza criteria, and the Classification criteria of Psoriatic Arthritis (CASPAR) are some of the frequently used. The CASPAR criteria are the most widely used with a high sensitivity and specificity but they are not ideal for early disease. Finally, the Assessment of SpondyloArthritis International Society (ASAS) developed peripheral and axial spondyloarthropathy criteria and PsA could be classified depending on whether axial involvement is present.

The diagnosis is made mostly on a clinical basis applying the above-mentioned classification criteria (CASPAR, ASAS). A detailed medical history, physical examination, blood tests and imaging techniques may help to diagnose PsA.

Imaging: conventional radiography (CR), computed tomography (CT), magnetic resonance imaging (MRI) and recently musculoskeletal ultrasound (MSUS) are all useful not only in the diagnosis but also for follow up of patients with PsA.

CR: any presence of bone destruction seen as erosions and bone proliferation seen as periostitis or even osteophytes can be seen by using plain x-rays. Other features can also be noted with CR such as bony ankylosis, distal tuft resorption, pencil-in-cup deformities, paravertebral new bone formation as well as sacroiliitis.

CT is a useful imaging modality with better resolution of the findings in comparison with CR. It is unable to detect active inflammatory lesions.

MRI is more sensitive than CR and CT in terms of detection of joint, periarticular and soft tissue inflammation. It can be used for the assessment of both peripheral and axial disease. Synovitis, enthesitis, tenosynovitis, periarticular inflammation, bone marrow oedema, bone erosions, bone proliferation, and sacroiliitis can be easily detected by MRI.

MSUS is a useful imaging modality in the everyday clinical practice. It can be used for the detection of peripheral joint involvement (synovitis and erosions) as well as periarticular involvement (enthesitis). Unfortunately, MSUS cannot be used in axial disease because its use is very limited in these structures.

Laboratory: *Full blood count (FBC):* in chronic cases, especially without treatment, anaemia of chronic disease is common in patients with PsA. It is also of great importance to exclude cases of occult blood loss from the gastrointestinal tract due to excessive use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Inflammatory markers: C-reactive protein (CRP) and the Erythrocyte Sedimentation Rate (ESR) are useful in the diagnostic workup but in approximately half of PsA patients are not elevated.

Autoantibodies: PsA is a seronegative arthropathy. Nevertheless, a positive Rheumatoid Factor (RF) as well as positive anti-Citrullinated Peptide Antigens (ACPA) can be found in low titre in a small percentage of patients (5–10% and 5% respectively). Anti-Nuclear Antibodies (ANA) can be present in about 25% of cases in low, clinically non-significant titres (1:40).

Synovial fluid: it is inflammatory, with cell counts ranging from 5000–15,000/ μ L and with more than 50% of cells being polymorphonuclear (PMN) leukocytes.

5.5 Management

PsA has a progressive and often destructive course. Thus, early initiation of therapy is desirable. As mentioned above, skin psoriasis precedes the onset of arthritis. Having this in mind, physicians should be suspicious with any new skeletal or extra-articular manifestations in order to be referred for appropriate investigations.

Mild forms of PsA can initially be treated with NSAIDs. Low-dose systemic corticosteroids (CS) can be utilised with rapid improvement of the symptoms from the skin and joints. Caution should be given to dose-reduction or discontinuation of CS due to the possibility of a fierce exacerbation, especially from the skin. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) can be used according to their therapeutic potency as far as it concerns the joints and the skin (methotrexate - MTX, cyclosporine - CSA, leflunomide - LEF). Finally, the treatment with tumor necrosis factor (TNF)-inhibitors as well as the newer cytokine inhibitors such as the interleukin (IL)-17 or the IL-12/23 but also the 4-phosphodiesterase inhibitors, have revolutionised the treatment of PsA.

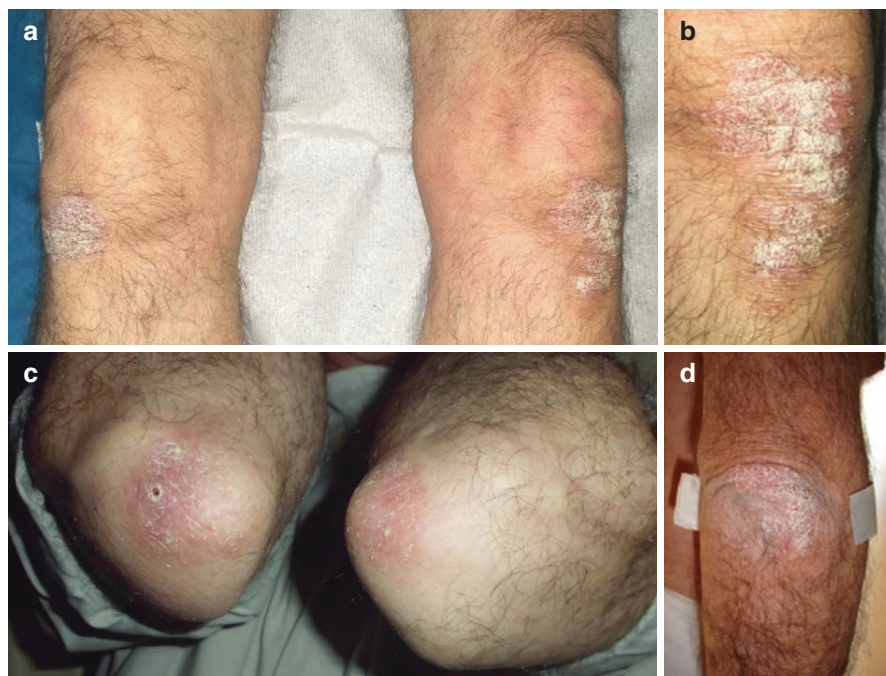


Fig. 5.1 Plaque psoriasis (psoriasis vulgaris) lesions

Skin manifestations in PsA usually precede arthritis in 70% of cases whereas arthritis precedes skin manifestations in about 15% of cases. Occasionally, both skin manifestation and arthritis appear simultaneously. Plaque psoriasis is the most common form. The typical rash consists of salmon-pink, scaly plaques on extensor surfaces. Typical anatomical regions affected are the knees and elbows (Fig. 5.1a–d), but any skin region can be affected as shown in Fig. 5.1e – thigh and Fig. 5.1f – periumbilical region. Skin lesions may be minimal, consisting of only a single spot a few mm in diameter to large confluent plaques covering large body areas (Fig. 5.2), if not the whole skin.

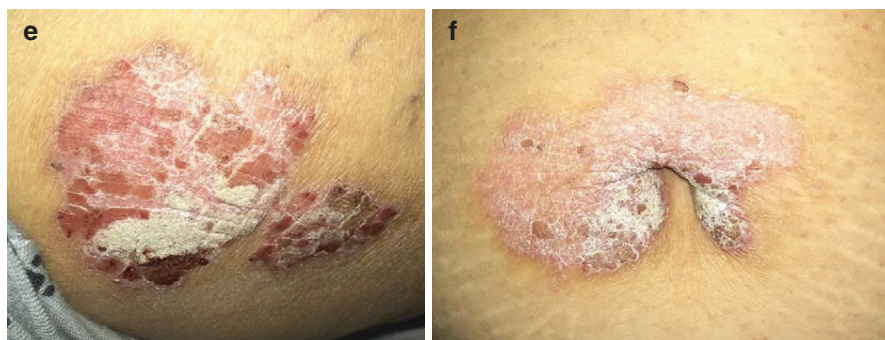


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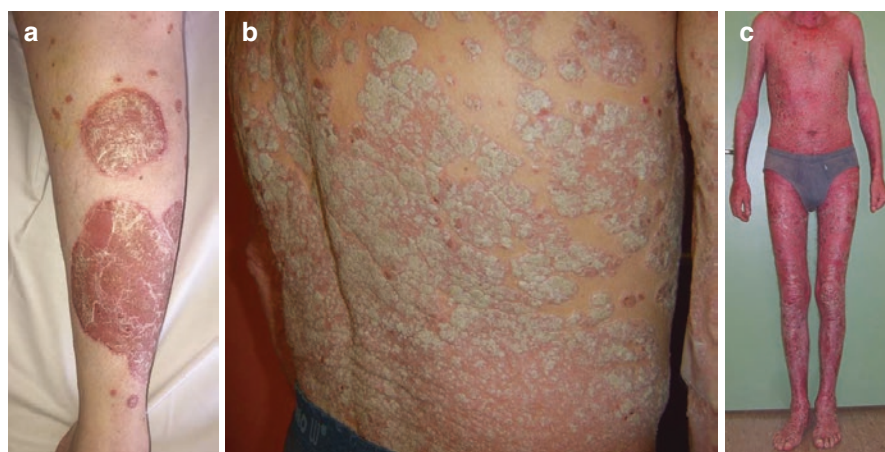


Fig. 5.2 Severe extent of skin lesions in psoriatic arthritis

As mentioned above, skin lesions may be minimal or they may affect the whole-body surface (Fig. 5.1a–c). PASI score (Psoriasis Area and Severity Index) takes into account, not only the extension of the skin lesions but also the severity of the lesions into a single score. The intensity or severity of redness (erythema), thickness (induration) and scaling (desquamation) of the psoriasis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4). The percentage area affected by psoriasis is evaluated in the four regions of the body (head: 10%, arms: 20%, trunk: 30%, and legs: 40%). For each body region a score from 0 to 6 is calculated (0: 0%, 1: <10%, 2: 10–29%, 3: 30–49%, 4: 50–69%, 5: 70–89%, 6: 90–100%). The total PASI score is 72. Severe psoriasis is defined when the PASI score ≥ 10 .

PASI score is widely used by the clinicians to assess the severity of the skin disease and for treatment planning strategies. It is also used in clinical trials in order to assess patients' response to treatment. This response is usually presented as a percentage response rate (PASI 50, PASI 75, PASI 90 etc.).

In Fig. 5.3, typical skin lesion paradigms are used in order to categorise the skin manifestation for a better understanding of the PASI score.



Fig. 5.3 PASI score (grading system)

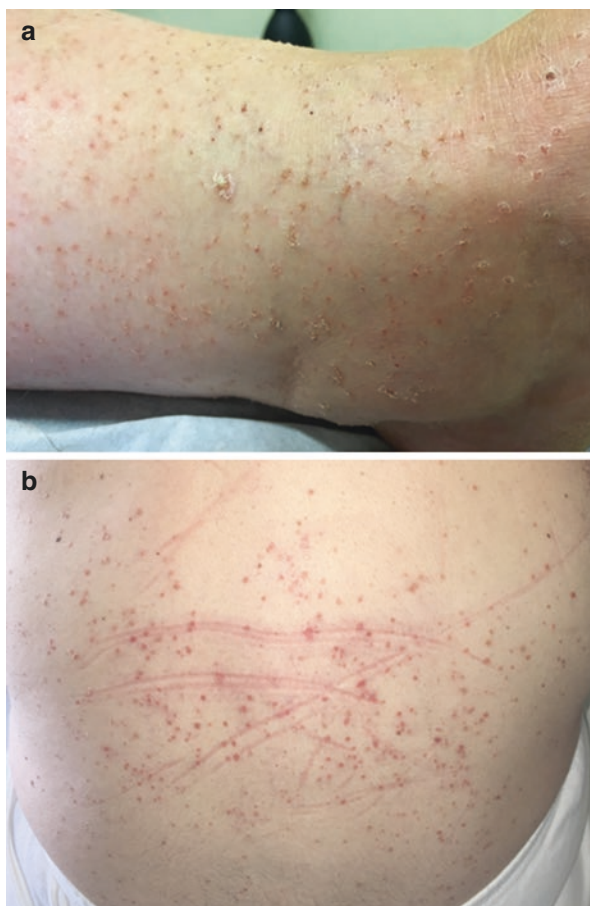


Fig. 5.4 Guttate psoriasis

Guttate psoriasis is a distinct form of psoriasis consisting of small drop-like scaly papules that present in an eruptive fashion on the trunk and proximal extremities.

This form of psoriasis is the second most-common type after plaque psoriasis and can be triggered by a bacterial infection, particularly group A streptococcal pharyngitis. In some cases, after treating the streptococcal infection with antibiotics and thus by reducing the triggering antigen, these psoriatic lesions disappear.

Patients with guttate psoriasis will develop chronic plaque psoriasis in a proportion of 10–20%. Usually, arthritis follows the psoriatic lesions.

In Fig. 5.4a, the lesions are finer in comparison with those in Fig. 5.4b. The diameter of the lesions is typically less than 1 cm.



Fig. 5.5 Koebner phenomenon

The Koebner phenomenon or isomorphic response is not pathognomonic for psoriasis as it can appear in other diseases (e.g. discoid lupus erythematosus), but is a common skin manifestation in psoriasis patients. It describes the appearance of new skin lesions on areas of minimal cutaneous injury (e.g. a scratch) in otherwise healthy skin. Note the linear minimal Koebner response.



Fig. 5.6 Inverse psoriasis

Most of the times, the psoriatic lesions spare the skin folds or appear on the extensor surfaces of the body. Inverse psoriasis or flexural psoriasis, is localised to the skin folds such as the axillae, groin, neck, popliteal region, and inframammary folds (Fig. 5.6a) but any skin fold may develop this kind of skin lesions. Usually they present as well-demarcated, thin erythematous plaques that lack the classic dry scale appearance because these areas are moist. As a result, the skin appears shiny but may also develop fine silvery scales at the edges (with less moisture, as seen in Fig. 5.6b – black arrows). These lesions may mimic intertrigo, candidiasis and tinea. Many patients have another type of psoriasis concomitantly.

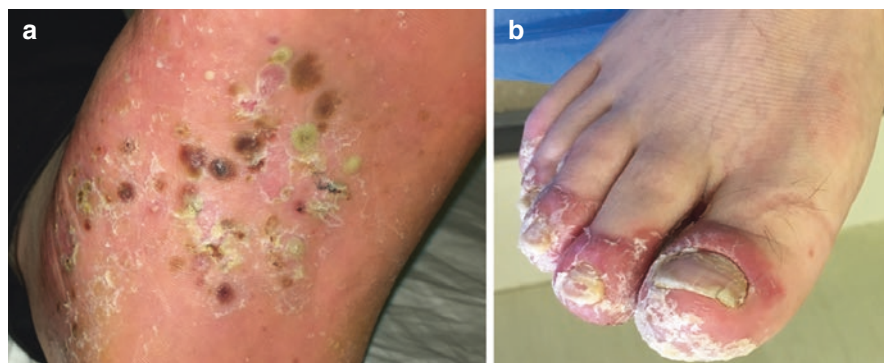


Fig. 5.7 Pustular psoriasis

This form of psoriasis is characterised by sterile pustules and can be generalised or localised. The localised form, as seen in Fig. 5.7a, is a less severe subtype of pustular psoriasis and usually affects the palms and soles. Figure 5.7b depicts a patient with a rare form of pustular psoriasis which is limited to the distal digits (acrodermatitis continua of Hallopeau) and it can be triggered by localised trauma or infection. 80% of cases begin in only one digit, and in severe cases it leads to anonychia.

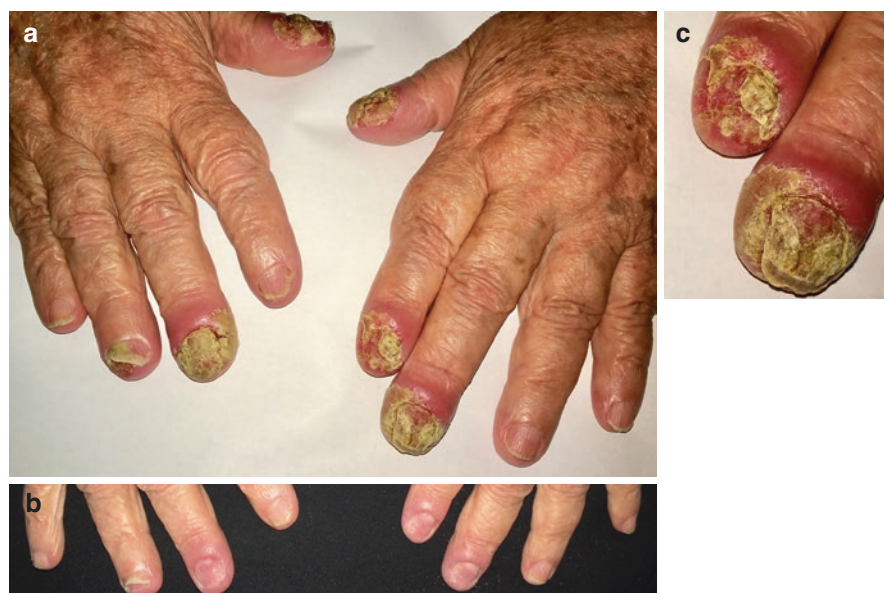


Fig. 5.8 Acrodermatitis continua of Hallopeau

As in Fig. 5.7b, this patient has a more severe form of acrodermatitis continua of Hallopeau with partial anonychia of the left index finger and destructive nail lesions of the middle fingers (Fig. 5.8a). Note the periungual inflammation. In these cases, fungal infections or other infectious causes must be excluded. In Fig. 5.8b, the same patient after 30 days of topical and systemic treatment with immunosuppressive agents. The psoriatic lesions of the skin have cleared with a mild periungual erythema to persist. There is also marked improvement of the nailbeds.

In Fig. 5.8c, acrodermatitis continua of Hallopeau of the second and third digits of the left hand in more detail.



Fig. 5.9 Erythrodermic psoriasis

Erythrodermic psoriasis is a rare and severe form of psoriasis that consists of generalised erythema covering of at least 90% of the total body surface area. Figure 5.9a–c are showing patients in different stages of the disease (*see also* Fig. 5.2c). Individuals having an erythrodermic psoriasis flare require hospitalization and initiation of systemic therapy given the risk of systemic complications, including fever, infection, dehydration, renal and high-output heart failure.



Fig. 5.10 Scalp psoriasis and “hidden” lesions

A thorough clinical examination should be carried out in all patients who complain about arthralgias and have a positive family history of seronegative spondyloarthropathies (SpA). The skin including the scalp should be examined in detail, because of the fact that lesions may be minimal or hidden. The scalp is a common location for hidden lesions. The patient in Fig. 5.10a had a small psoriatic plaque on the scalp. Multiple discrete plaques or involvement of the entire scalp are not uncommon manifestations of scalp psoriasis. The thickest plaques can be observed at the occiput. Despite the severity of the lesions, alopecia is uncommon. Other common sites of “hidden” lesions are the retroauricular region – Fig. 5.10b, c, ear (external auditory meatus – Fig. 5.10d), natal cleft and umbilicus. Note also the psoriatic plaque on the scalp in Fig. 5.10d.



Fig. 5.11 Pitting of the nails and onycholysis in psoriatic arthritis

Nails are affected in a large proportion of patients with PsA. Pitting (Fig. 5.11a, b – black arrows) is occasionally helpful in building a clinical case for PsA, in the absence of other definitive markers, especially where it is the only cutaneous manifestation of psoriasis. Isolated nail involvement with more than 20 pits are suggestive of having a psoriatic aetiology. In Fig. 5.11a–d, different patients with pitting of the nails are shown. A quantifiable assessment of nail involvement in psoriatic patients can be achieved using the NAPSI score (Nail Psoriasis Severity Index). Onycholysis (Fig. 5.11e–g – yellow arrows), is also a common feature, but it is considered to be a more severe involvement. More than one nail manifestation can coexist. In Fig. 5.11e and g, nail pitting, onycholysis and hyperkeratosis (yellow dashed circles) are shown.

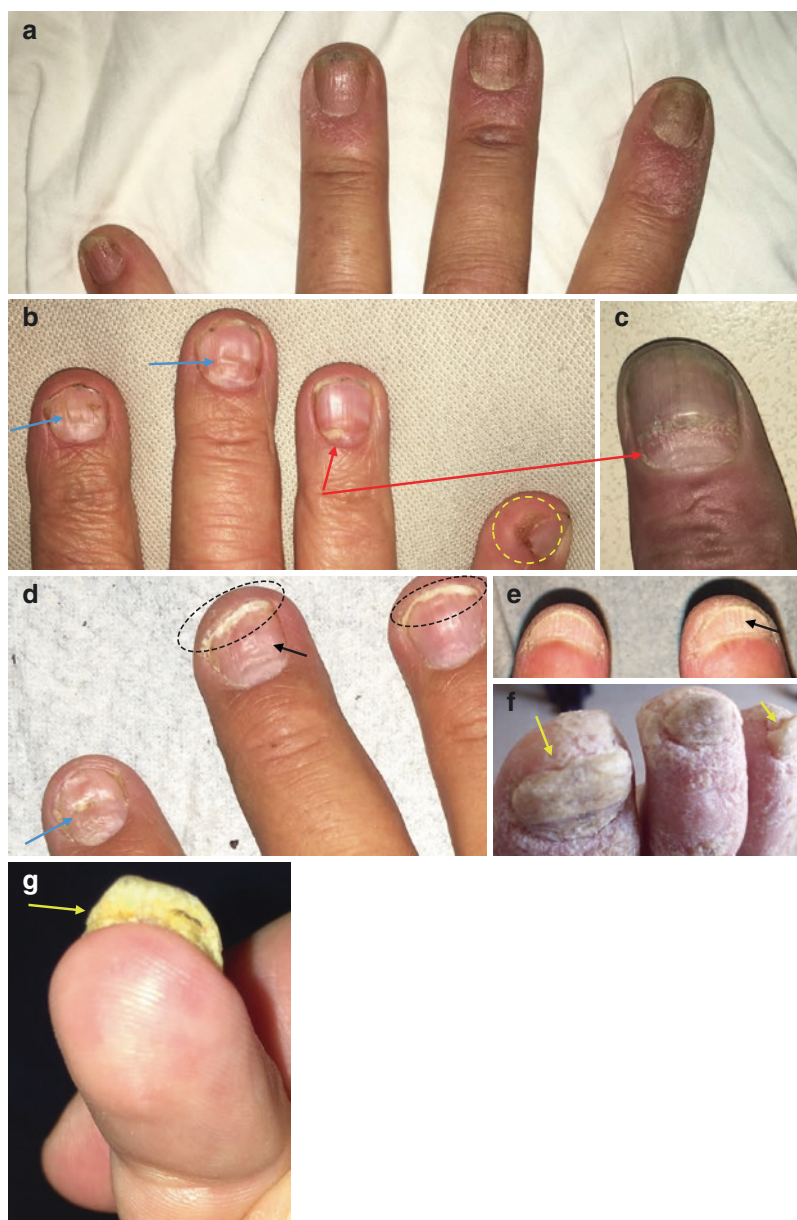


Fig. 5.12 Nail involvement in psoriatic arthritis

In Fig. 5.12a nail pitting and discoloration of the nails are evident. Different nail disorders may be present concomitantly such as in Fig. 5.12b. Beau's lines (blue arrows), onychomadesis (red arrows – see also Fig. 5.12c) and chronic paronychia (yellow dashed line). Another patient with different nail manifestations, onycholysis (black dashed circles), nail pitting (black arrow) and Beau's lines (blue arrow – Fig. 5.12d). Brachyonychia is another not so common manifestation. Note also the nail pitting (Fig. 5.12e). For unknown reasons, nail pitting and onycholysis typically appear on the fingers, while hyperkeratosis appears typically on the toes (Fig. 5.12f, g – yellow arrows). Nails, as accessory structures of the skin, present a rich pathology in PsA patients and should always be examined thoroughly.



Fig. 5.13 Dactylitis (sausage digit) in psoriatic arthritis

Dactylitis, has long been recognised as one of the cardinal features of PsA. It is characterised by swelling of a whole digit and represents a combination of synovitis and inflammation of tendon and ligament insertions. It is not a pathognomonic feature of PsA as it is common in the other SpA as well.

Toes (Fig. 5.13a) are affected more frequently than fingers in a proportion approximately 3:1. Many studies point out that dactylitis is associated with a greater degree of radiological damage than occurs in the non-affected digits. In Fig. 5.13b a patient with severe psoriasis and dactylitis affecting the middle finger of both hands is shown (*see also chapter of ankylosing spondylitis (AS) for chronic dactylitis figures*).

The Leeds Dactylitis Instrument (LDI) has been developed in order to quantify dactylitis. It measures the ratio of the circumference of the affected digit to the circumference of the digit on the contra-lateral hand of foot.

A minimum difference of 10% is used to define a dactylitic digit. In case the contra-lateral digit is also affected, a table of normative values based on population averages is used to provide the comparison.



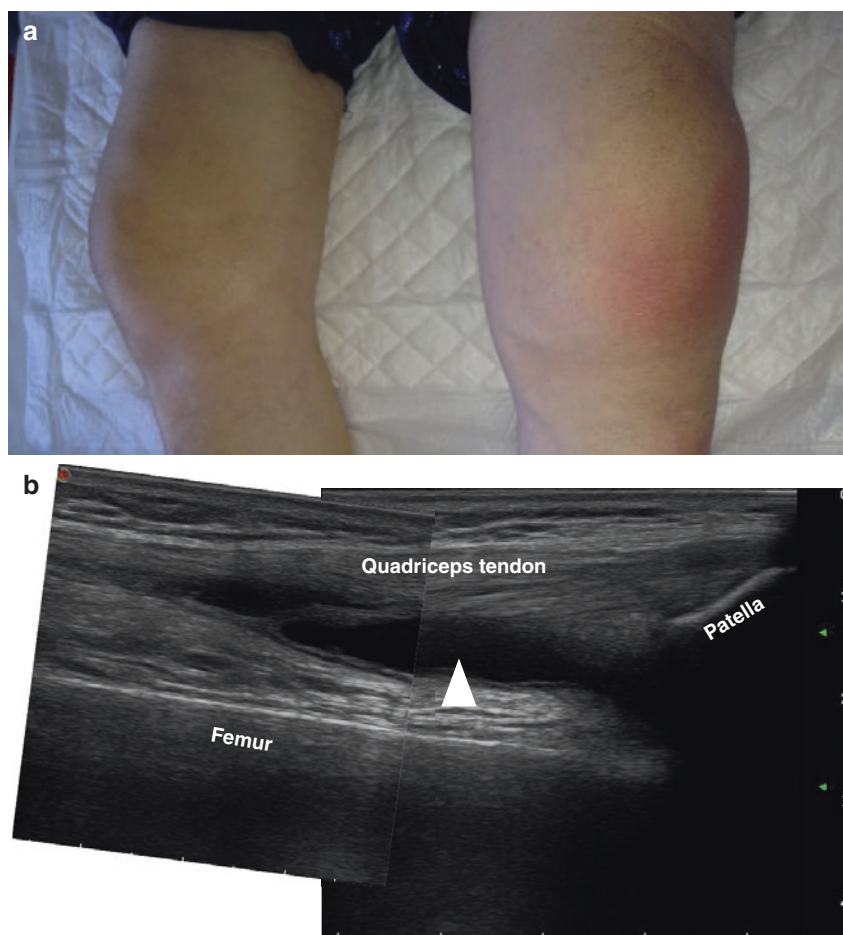


Fig. 5.15 Monoarthritis in psoriatic arthritis (knee)

Acute monoarthritis may be the initial manifestation of many joint disorders. A careful history and examination are important because diagnostic studies frequently are only supportive. In such cases, examination of joint fluid is essential. Crystal arthropathies, trauma, infection and inflammatory disorders may be the cause. Although in patients with PsA there is preexisting symptomatology from the skin and nails years before the involvement of the musculoskeletal system, in some cases, acute monoarthritis may be the initial symptom. In Fig. 5.15a, a patient with acute monoarthritis of the left knee is shown. Synovial fluid analysis revealed 19,400 leucocytes per mm^3 with no crystals. Figure 5.15b, shows a collection of synovial fluid in the suprapatellar synovial recess (white arrowhead) with the use of MSUS in an anterior longitudinal scan of the knee joint.



Fig. 5.14 Psoriatic arthritis – pseudorheumatoid deformities

Some patients may develop a subtype of PsA that resembles rheumatoid arthritis (RA). This patient in Fig. 5.14 has some features of RA such as mild metacarpophalangeal (MCP) subluxation, swan-neck-like deformity of the index finger, z-shaped thumb and a mild ulnar drift.

Differentiating RA from PsA may prove more challenging, especially in those psoriatic patients with rheumatoid-like polyarticular involvement, but the history or the presence of psoriasis may help to differentiate between these two entities.



Fig. 5.16 Achilles tendonitis

Achilles tendon involvement occurs in a significant number of patients with long-standing PsA as compared to newly diagnosed cases. It has been reported that Achilles tendonitis can affect 10–30% of psoriatic patients. Patients complain of severe heel/foot pain and difficulty in walking. A thorough clinical examination reveals swelling and tenderness along the course of the tendon and at the calcaneal insertion. Imaging techniques such as MSUS and MRI are useful tools to diagnose this condition as early as it is asymptomatic. In this figure, a significant swelling of the right Achilles tendon is shown, but the left side is also affected.

Fig. 5.17 Achilles tendonitis

PD mDIXON image on MRI in sagittal plane revealed diffuse fusiform thickening (white thick arrows) in full length of the Achilles tendon (AP diameter 15 mm, normal <6 mm) with no tear or enthesitis.



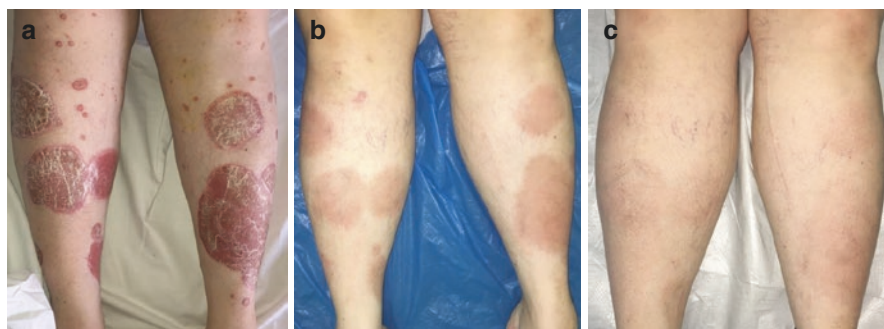


Fig. 5.18 Psoriatic arthritis patients before and after treatment – case nr. 1

A case of recalcitrant psoriatic arthritis and plaque psoriasis to csDMARDs and TNF-inhibitors, treated with an IL-17a inhibitor. Figure 5.18a–c show the improvement of the skin lesions on day 1, 2 months and 6 months after treatment respectively. Note that the psoriatic plaques have almost disappeared. The patient reported improvement of the joints as well.



Fig. 5.19 Psoriatic arthritis patients before and after treatment – case nr. 2

This 60-years-old patient presented to the outpatients' clinic with severe skin lesions and a PASI score of >30. He also presented severe arthritis and dactylitis (Fig. 5.19a). He received treatment with intravenous infliximab. Figure 5.19a–c show the improvement of the skin lesions after 1 month (b) and after 2 months (c). Note also the improvement of the nails. Dactylitis has almost disappeared and a slight redness on the site of the skin lesions has remained. He reported no stiffness or arthralgias after treatment.

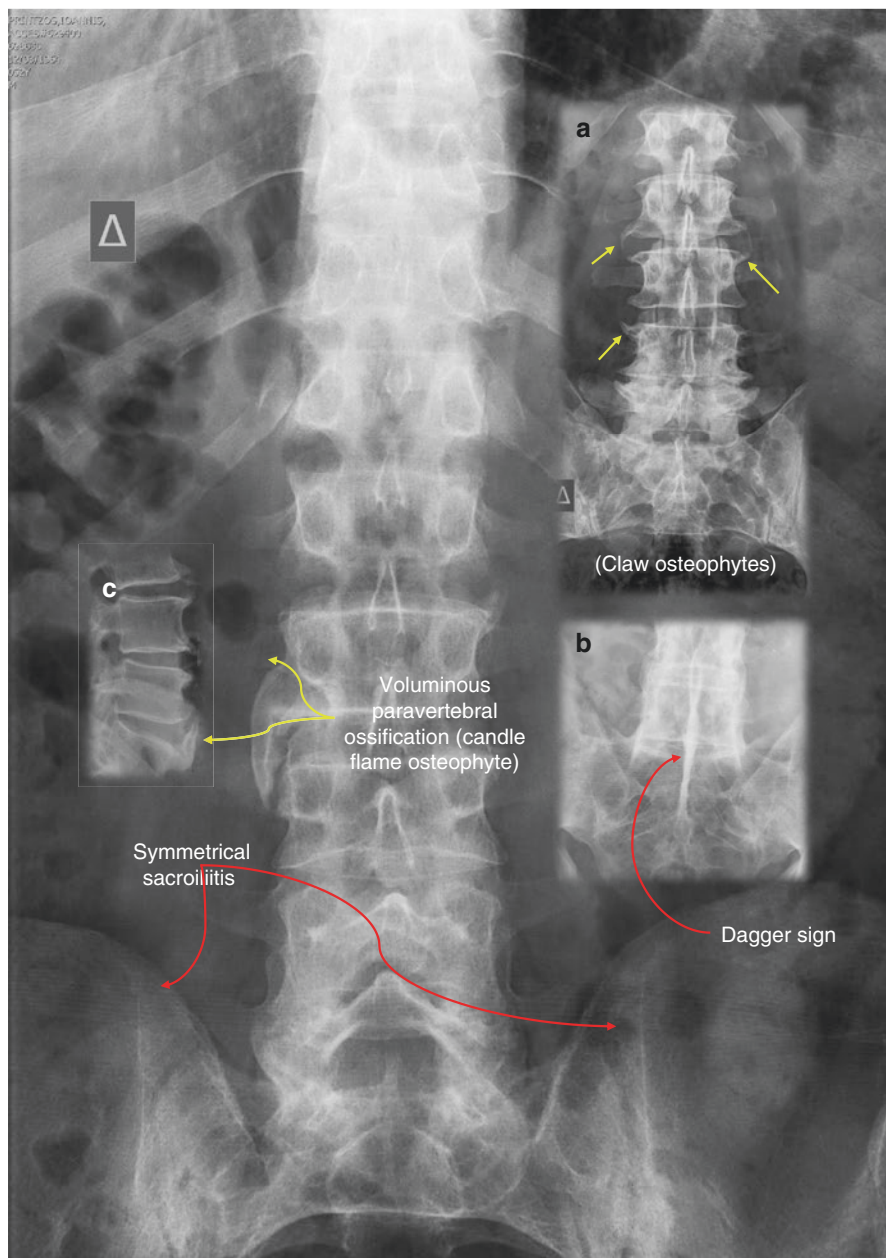


Fig. 5.20 Radiographic findings – lumbar spine

Axial involvement is not uncommon in PsA. In this Figure, lumbar spine x-rays of different patients are shown. The characteristic features of the disease are the asymmetric paravertebral osteophytes (Fig. 5.20a – yellow arrows) or unilateral sacroiliitis, but other features of PsA may resemble those of AS. In Fig. 5.20b, the dagger sign is evident due to ossification of the supraspinous and interspinous ligaments. This is a characteristic feature of AS but it can also be present in PsA patients. In Fig. 5.20c and the background figure voluminous ossifications are seen. As stated above, the sacroiliac joints are involved in an asymmetric fashion, but as seen in the background figure, symmetrical sacroiliitis is a possible finding. (See the chapter of AS to compare those findings).

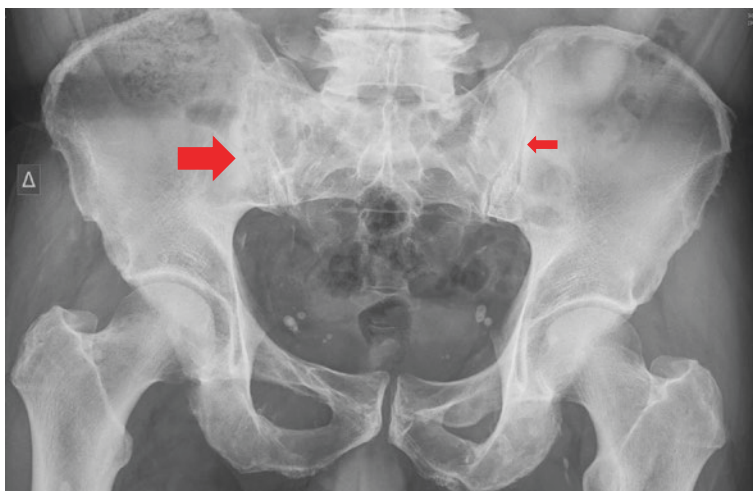


Fig. 5.21 Radiographic findings – sacroiliac joints

Approximately 25% of patients with PsA present a degree of sacroiliac joint involvement. Usually, the sacroiliac joint develops unilateral or bilateral changes. Typically, the involvement is unilateral.

Figure 5.21 shows a patient with a bilateral asymmetrical involvement of the sacroiliac joints (right > left).

The sacroiliac joint involvement may be similar to that seen in AS. MRI can detect signs of active inflammation as well as chronic structural changes and it is of superior diagnostic importance in comparison with plain x-rays.

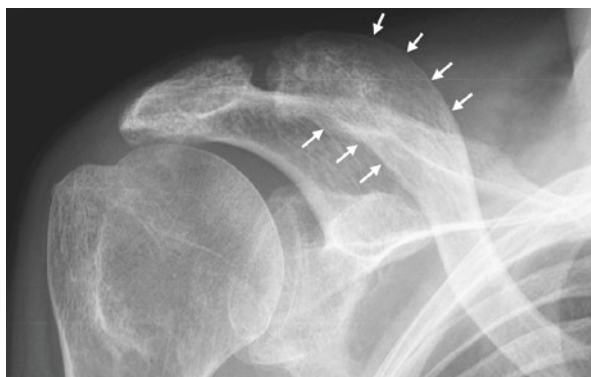


Fig. 5.22 Radiographic findings – acromioclavicular joint

Anteroposterior view of the shoulder in a patient with PsA. Note the exuberant bone formation especially on the acromial end of the right clavicle (white arrows). Tendon and ligamentous attachments are common sites of new bone formation. This is an uncommon finding in PsA involving the shoulder.

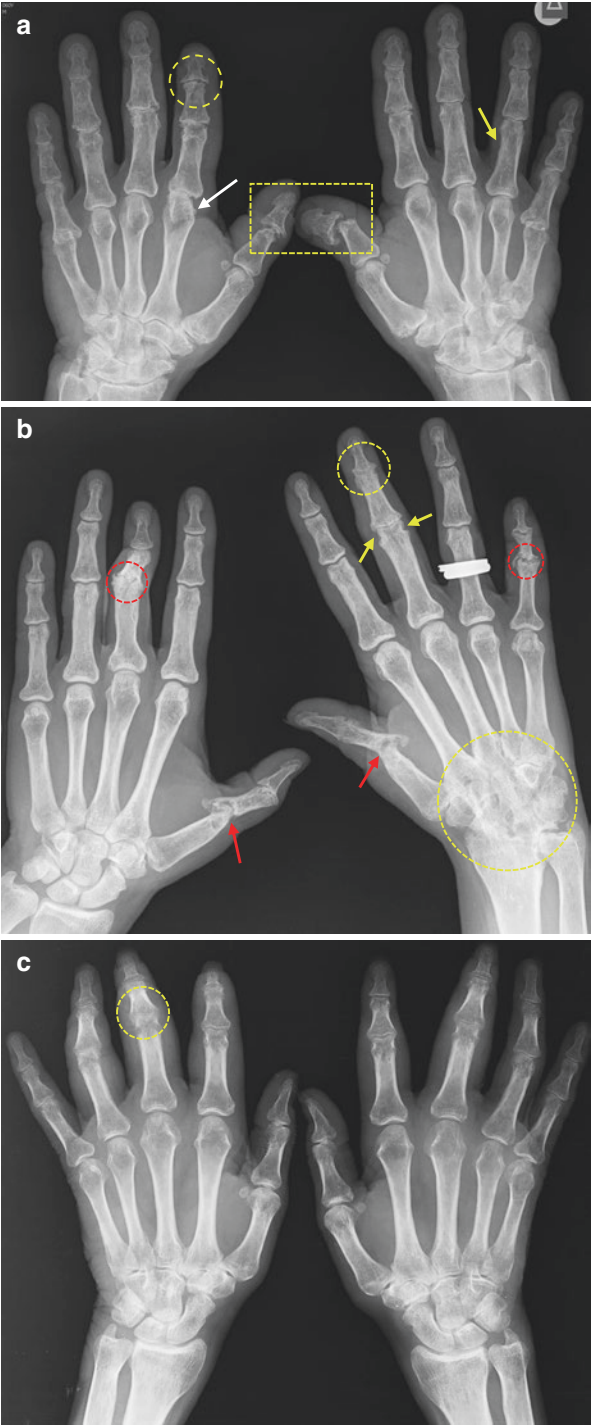


Fig. 5.24 Ivory phalanx

This radiological finding on a plain radiograph is consistent with the so called “ivory phalanx”, a characteristic sign of PsA patients. It is related to periosteum and endosteum condensation with trabecular thickening, leading to an increase in the radiological density of the phalanx. Typically, it affects the great toe but any of the phalanges may be affected. It is likely the result of bony proliferation as an exaggerated healing response to injured bone. In this figure the middle finger is affected.

Note also the erosion of the 1st MCP joint.

**Fig. 5.23** Radiographic findings – hands

The hands are commonly involved in PsA patients. The characteristic finding is the asymmetrical pattern of the erosions.

Figure 5.23a sausage-like swelling of the 1st and 2nd digits (left). Proximal interphalangeal (PIP) joints and DIPs are affected in an asymmetric pattern. Carpal bones are also affected. The interphalangeal (IP) joints of the thumbs have the characteristic finding in PsA called the “pencil-in-cup” deformity (yellow rectangle). The DIP of the left index finger has an early pencil-in-cup deformity (yellow circle). Periostitis is a common finding in PsA and usually it is best seen along the shafts of the bones (yellow arrow). Bone proliferation on 2nd MCP (white arrow) along with joint space narrowing. Bone proliferation is one of the most important features of PsA and is almost always present in some form.

Figure 5.23b asymmetry of erosions. Bone ankylosis of the 3rd right DIP joint and right carpal bones with pancarpal involvement and severe erosions of all the carpal bones (small and big yellow circles). Marginal erosions of the 3rd PIP joints (yellow arrows). Erosions occur initially at the margins of the joint but with time progress to involve the central area (red circles: 3rd PIP of the left hand and 5th PIP of the right hand). Note also the pencil-in-cup deformities of the 1st MCPs and the 5th digit of the right hand which is shorter than the contralateral.

Figure 5.23c severe sausage-like swelling of the 2nd, 3rd, 4th digits of the left hand and 2nd, 3rd of the right. Bone ankylosis is best seen on the 3rd PIP joint of the left hand (yellow circle). Note also periarticular osteopenia involving the 3rd and 4th MCP's of the right hand.

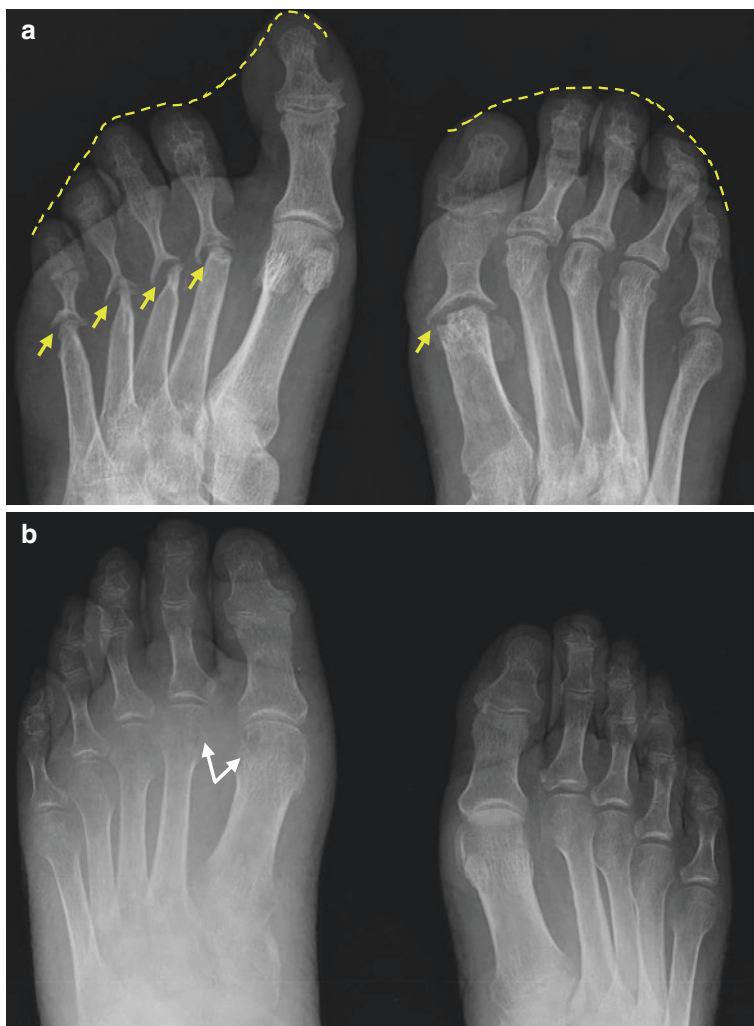


Fig. 5.25 Radiographic findings – feet

The feet present the same radiographic changes described in the hand. The main characteristic is the asymmetry of the lesions.

Figure 5.25a severe erosions with different distribution between the two feet. On the left foot, pencil-in-cup deformities on 2nd – 5th metatarsophalangeal (MTP) joints with subluxations and on the 1st MTP of the right foot (yellow arrows). As a result, the length of the toes is different between the feet (yellow dashed lines). There are also erosions on the DIP joints and bone proliferation with marginal erosions especially on the great toes.

Figure 5.25b asymmetric DIP involvement and erosions on the 1st and 2nd MTPs (white arrows) of the left foot. Note the sausage-like swelling of the 1st and 2nd toe.

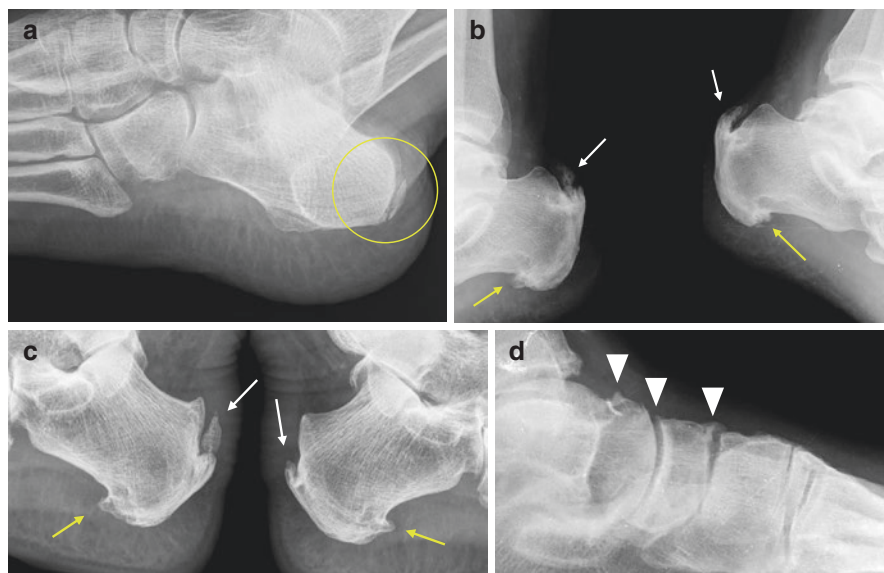


Fig. 5.26 Radiographic findings – enthesophytes

Enthesitis is a characteristic feature of seronegative arthritis.

Enthesophytes or enthesiophytes are abnormal bony projections consisting of calcification deposits and usually are found at the attachment of a tendon or ligament. The entheses of the lower limbs are more commonly affected than those of the upper limbs. Calcaneal enthesitis is one of the most commonly affected (plantar fascia and Achilles' tendon insertion). Large enthesophytes are associated with PsA and diffuse idiopathic skeletal hyperostosis (DISH) whereas more thin ossifications are usually seen in patients with AS but the distinction between those pathologies is difficult. In Fig. 5.26a note a medium-sized enthesophyte within the Achilles tendon at its calcaneal insertion. In Fig. 5.26b and c, more severe cases are shown, with large osteophytes bilaterally at the back of the heels (dorsal heel spurs – white arrows) and under the sole (plantar heel spurs – yellow arrows). In Fig. 5.26d there is enthesophyte formation seen associated with the intertarsal joints (white arrowheads).

Fig. 5.27 Comorbidities in psoriatic arthritis – Crohn's disease

People with PsA are at greater risk of developing various comorbidities such as cardiovascular disease, depression, uveitis, Crohn's disease and other health conditions.

There is a clear connection between PsA and inflammatory bowel disease such as Crohn's disease or ulcerative colitis but with a predilection to the former. Aphthous erosions with stellate ulcers mixed with normal mucosa are the characteristic findings of patients suffering from Crohn's disease as in this figure. Sometimes, inflammatory bowel disease may precede PsA.



Fig. 5.28 Comorbidities in psoriatic arthritis – xanthelasma palpebrarum

Xanthelasmata (black arrows) is a skin condition that occurs on the eyelid or periorbital skin as yellowish plaques (Fig. 5.28a upper eyelid, Fig. 5.28b upper and lower eyelid). In the recent past, a link between dermatological disorders like psoriasis and dyslipidaemia has been established. Multiple cardiovascular risk factors are also associated with psoriasis and several studies have demonstrated that the prevalence of metabolic syndrome is significantly higher in patients with psoriasis and PsA as compared to controls. Thus, the metabolic profile of patients with PsA should be checked and treated appropriately to lower the cardiovascular risk in such patients.



Fig. 5.29 Comorbidities in psoriatic arthritis – hidradenitis suppurativa

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, difficult to treat skin disease primarily affecting the axillae. Other regions affected by HS are the groin, perineum, breasts and buttocks. It is characterised by outbreaks with painful nodules and recurrent abscesses (Fig. 5.29a) that may lead to fistulas. The nodules are filled with pus (Fig. 5.29b). If the treatment with topical and oral antibiotics fails, then adalimumab, a TNF-inhibitor may show effectiveness in the management of refractory cases. HS and skin psoriasis in patients with psoriatic arthritis seem to share common pathogenetic pathways. The exact prevalence of the disease varies between ethnic groups and is not well studied across the globe. International bibliography lacks specific characteristics of patients with concomitant HS and PsA. Nevertheless, smoking is a known factor that promotes inflammatory conditions and from small studies nearly 50% of those patients are smokers. In addition, women seem to be frequently affected in comparison with men. Finally, a high body mass index (BMI) seems to be correlated with the appearance of these two clinical entities.

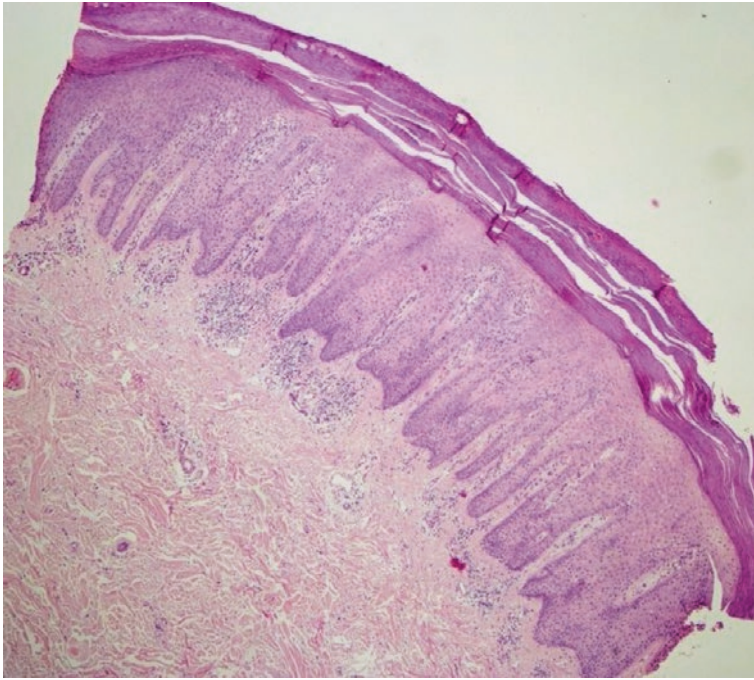


Fig. 5.30 Psoriasis – histopathology

Psoriasiform hyperplasia with rete ridges of equal length, thin suprapapillary plates, granular zone absent, confluent parakeratosis with neutrophils in collections, thin dermal papillae and moderately dense perivascular lymphocytic infiltrate in the upper part of the dermis (H-E $\times 40$).

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Chapter 6

Ankylosing Spondylitis



6.1 Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that affects the spine and the sacroiliac joints (SI). It makes part of the “seronegative spondyloarthropathies” or spondyloarthritides (SpA). SpA describes a group of inflammatory arthritis diseases that are clinically and genetically related, but have distinct features from one another.

The first clinical descriptions of the disease date from the late nineteenth century, and the medical interest in AS was stimulated by a series of publications in the 1890s by the Russian neurophysiologist Vladimir von Bechterew in St. Petersburg, Russia. About the same period the German neurologist Adolph Strümpel (1897) and the French neurologist Pierre Marie (1898) also gave adequate descriptions of the disease. The terms Bechterew’s disease and Marie-Strümpel disease were used interchangeable at that time.

6.2 Epidemiology

The prevalence is between 0.1% and 0.2% of the general population. The disease is most prevalent in Northern European countries, and seen least in people of Afro-Caribbean descent. The male to female ratio is 4–5:1, however many rheumatologists believe the number of women with AS is underdiagnosed, as most women tend to experience a milder form of the disease. The majority of people with AS express the Human Leucocyte Antigen (HLA)-B27 and high levels of immunoglobulin A in the blood. It appears usually between the ages of 15 and 45.

6.3 Aetiopathogenesis

The genetic hypothesis involved in AS was first reported during the years 1950–60 on familial aggregation studies. In 1973, the association of HLA-B27 with the development of AS was reported. Twin studies in AS have shown a monozygotic concordance rate of around 70%. Several lines of evidence suggest that HLA-B27 heavy chains can form homodimers that do not contain the β 2-microglobulin light chain (HLA-B27 misfolding phenomenon). Such homodimers could mediate, or be the target for a proinflammatory response.

AS is marked by enthesitis, synovitis and osteitis involving mostly the axial skeleton particularly the sacroiliac joints. To this end, infection of the gastrointestinal or genitourinary tracts have been implicated as triggers of HLA-B27 associated reactive arthritis. These include *Campylobacter*, *Chlamydia*, *Salmonella* and *Shigella*

spp. Several lines of evidence implicate the cells and molecules of innate immunity to participate in the pathological pathway involving CD4⁺, CD8⁺ cells, interleukin (IL)-2, IL-17, but also tumour necrosis factor (TNF).

6.4 Classification Criteria

AS is the prototype of inflammatory rheumatic diseases grouped under the term SpA. An early diagnosis has become increasingly important because effective therapies are available and anti-TNF inhibitors are even more effective if used in early stages of the disease. The 1984 modified New York criteria have been used widely in clinical studies and daily practice, but are not applicable in early disease. New classification criteria for the wider group of SpA have been proposed by the Assessment of SpondyloArthritis International Society (ASAS). The new classification criteria have two arms: the imaging arm and the clinical arm. The imaging arm requires presence of sacroiliitis as detected by conventional radiography or by magnetic resonance imaging (MRI) and at least one of the clinical features of SpA [inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), family history for SpA, HLA-B27, elevated C-reactive protein (CRP)]. The clinical arm requires presence of HLA-B27 and at least two of the clinical features.

6.5 Signs and Symptoms

Inflammatory back pain is the hallmark of AS. It is of significant importance to differentiate inflammatory from non-inflammatory causes of back pain, because the latter is not an uncommon complaint in the general population. The character of the former is characterised by pain and stiffness that is worse in the morning hours after waking up or after long periods of inactivity (sitting in a chair or driving) and improved with exercise (gel phenomenon). Another characteristic that seems to be a more specific finding for inflammatory back pain, is the alternating buttock pain which usually represents sacroiliac involvement. Patients commonly complain that pain is not relieved with rest and can be disturbing when lying down to sleep. Peripheral arthritis is observed in about 10–20% of patients with AS mainly as mono- or oligoarthritis or asymmetrical polyarthritis. Dactylitis involving multiple joints of the same digit is also present as well as enthesitis. The most typical site of enthesitis is the Achilles tendon insertion with heel pain which may be posterior or inferior to the insertion. Other findings/complaints such as skin psoriasis, bowel problems and uveitis may help in diagnosis.

6.6 Differential Diagnosis

Mechanical disorders are the most common causes of low back pain. They include muscle strain, herniated nucleus pulposus, spinal stenosis, osteoarthritis (OA), spondylolisthesis and scoliosis. The differential diagnosis includes also patients with systemic disorders and back pain having also: fever, weight loss, pain with recumbency, localised pain or visceral pain. The patient's symptoms and physical signs help the physician to differentiate mechanical from systemic causes of axial pain. Thus, a detailed history and physical examination with complete evaluation of the musculoskeletal system, including neurological examination is needed. In most patients, plain radiographs, full blood count (FBC) with differential, erythrocyte sedimentation rate (ESR), CRP are the most informative examinations. In older patients with constitutional symptoms or with a history of cancer or infection a detailed clinical and laboratory investigation should be performed.

The differential diagnosis of cervical and lumbar spine involvement in AS includes also diffuse idiopathic skeletal hyperostosis (DISH) in which, unilateral bulky bridging spondylophytes mimicking mixed syndesmophytes. There is also extensive calcification of the anterior spinal ligament. Other disorders to differential from AS are the degenerative spine diseases, as well as kyphoscoliosis which have distinct clinical and radiological features including vertebral joint space narrowing, osteophyte formation, spinal stenosis and others.

6.7 Diagnostic Modalities

Physical examination: it is of utmost importance to examine thoroughly the spine. A simple inspection of the patient may give important information about the status of the disease. Increased thoracic kyphosis may lead in a stooped posture with a forward set head position and difficulty in looking upwards. Flexion, extension, lateral flexion and rotation of the spine, all give significant clues. Other tests during the physical examination include the occiput to wall distance, chest expansion, the modified Schober test, sacroiliac compression testing.

Imaging: pelvic radiographs are essential to make the diagnosis of AS. Sacroiliitis is the required and the earliest radiographic manifestation. The classic finding of squaring of the vertebral bodies is another important radiological finding. Syndesmophytes resulting from the ossification of the spinal ligaments may give the appearance of the so called "bamboo spine" (late sign).

Computed tomography (CT) and MRI can be used at the early stages of the disease with considerably higher sensitivity in identifying sacroiliitis. More specifically, CT appears to be superior to MRI for the visualization of chronic bony changes, whereas MRI technique is better than CT in revealing early cartilage changes and bone marrow oedema. With the help of MRI, inflammatory changes in the SI joints can be identified years before appearance of radiological changes using the conventional X-ray films.

6.8 Radiographic Changes

The first radiographic changes observed in AS are found in the SI joints. The joints are involved bilaterally and symmetrically. AS is an ossifying disease. It will ossify the ligaments that join the sacrum to the ilium. The diagnosis of disease involving the SI joints depends upon observing the following: the width of the joint space, the presence and type of erosions, the presence and type of sclerosis, the presence and the type of bone bridging and the distribution of the above changes.

The erosions are seen first on the iliac side and then on the sacral side. The erosions are small, giving the joint edge the appearance of the perforated edge of a postage stamp. The erosions are surrounded by a small amount of bone repair. As the process continues the SI joint space is diminished, bone repair and sclerosis increases, and SI joints are completely fused and ankylosed.

Initial involvement of the spine may be seen in the T12 to L1 area. It is then seen to progress upward through the thoracic spine to the cervical spine. Initially there is erosion of the corner of the vertebral body (Romanus lesion) with secondary reactive sclerosis. This gives a squared appearance to the vertebral body, and the reactive sclerosis is identified as the “ivory corner” or shiny corner ossification, first take place in the outer portion of the annulus fibrosus or in Sharpey’s fibers. This ossification will extend then into the deep layers of the longitudinal ligaments and ossifies one vertebral body to the adjacent vertebral body in a symmetrical fashion involving the thoracic and the cervical spine.

Anderson lesions or spondylodiscitis is an inflammatory process of the intervertebral disc observed in AS. Plain radiography depicts irregularities and erosions of the vertebral end plates that are not related to the anterior or posterior edge, but rather to the central portion of the vertebra. Finally, arthritis of the facet joints and enthesitis are typical changes of the vertebral spine in AS.

Thus, AS related radiographic pathology in the spine and joints are as follow: erosions, sclerosis, joint space narrowing, blurring of joint margins, spurs, bony fusion, bony bridging, calcification, syndesmophytes, spondylophytes and spondylodiscitis.

6.9 Management

Regular exercise may slow the progression of spinal stiffness and restriction. NSAIDs are the first pharmacological approach for AS with spectacular results at the early stages. It has been demonstrated that conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) are ineffective in the treatment of patients with axial involvement but they may prove effective for the inflammation of the peripheral joints. TNF-inhibitors have offered new perspectives for AS patients, with impressive improvements of their clinical outcome. Finally, other biological drugs have been developed such as Interleukin (IL)-17A inhibitors.

Romanus lesion: erosions of the corner where the annulus fibrosus attaches.

Shiny corners: sclerosis of the adjacent bone.

Syndesmophytes: bone proliferation and ossification of the annulus fibrosus resulting in vertical outgrowths.

Anderson lesion: is an inflammatory process affecting the intervertebral disc.



The line joining the superior aspect of the iliac crests posteriorly (the intercrystal line) is commonly used as a landmark in order to find the L4–L5 vertebral bodies. Another useful anatomic landmark is the “Dimples of Venus” that are located approximately at the same level with L4–L5.

Fig. 6.1 Postural changes

Characteristic postural changes in patients with AS. The “hang-dog” posture or the “question mark” posture, is the result from rounding of the shoulders and a slight dorsal kyphosis (Fig. 6.1a). Patients with AS have limited spinal motion in all directions. In Fig. 6.1b there is a significant loss of the ability to bend laterally when the patient is asked to touch the lateral side of the knee. Figure 6.1c shows the characteristic limited spinal flexion which can be quantified using the Schober’s test or the modified Schober’s test*. Patients are not able to touch their toes. This patient had a positive Schober’s test (+3 cm).

*Schober’s test (ST) and the Modified Schober’s test (MST) are used to measure the ability of a patient with AS to flex the lower back. MST is performed with the patient in a standing position. The examiner draws a mark at the level of L4–L5 and then two further points, 5 cm below and 10 cm above this mark (total 15 cm). Then, the patient is asked to touch his toes while keeping the knees straight and the examiner measures the distance between the two points at the maximum flexion. If the distance does not increase by 5 cm, then the test is considered positive. The ST can be done with the same method using an additional line above the L4–L5 level.

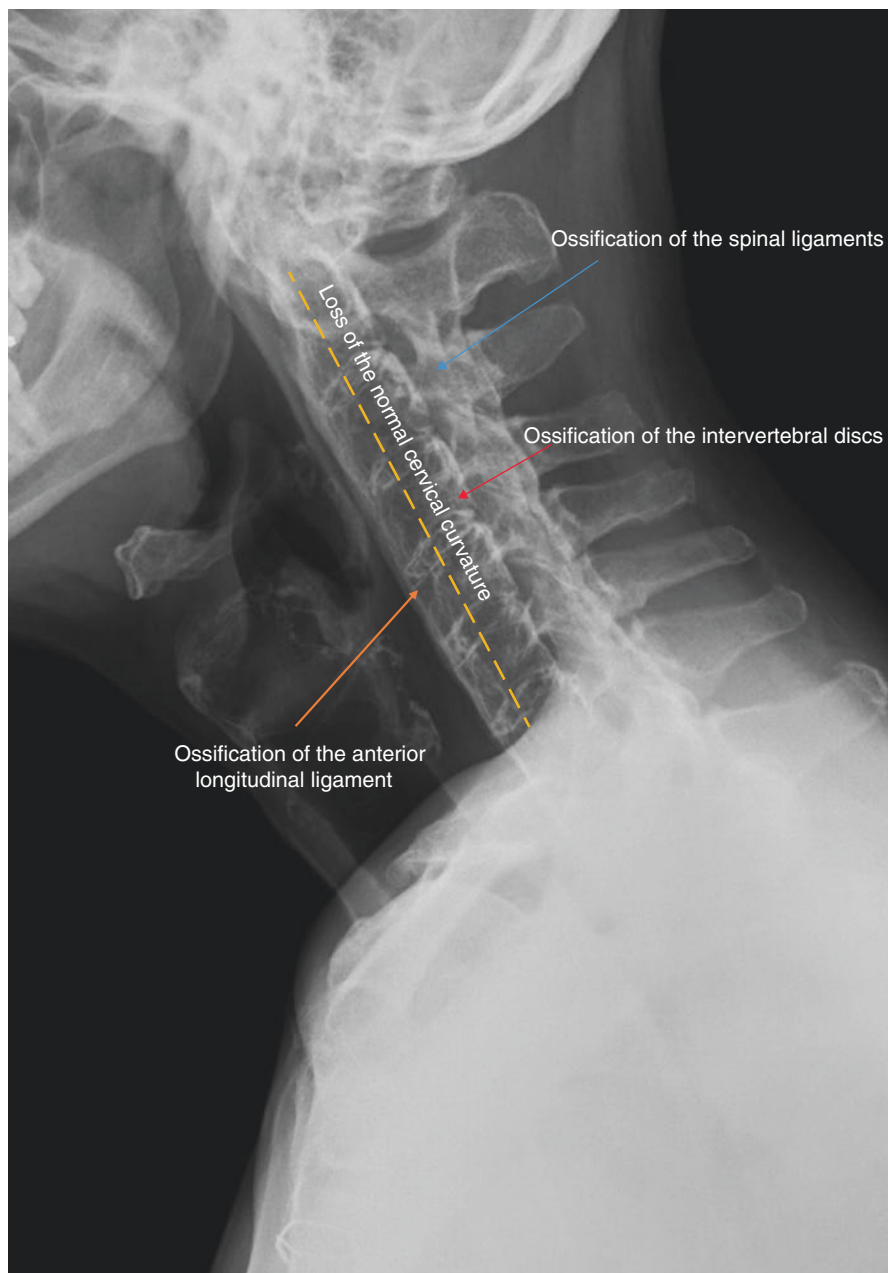


Fig. 6.2 Bamboo spine (neck) with ossification of the spinal ligaments and discs. Note the loss of the physiologic curvature of the cervical spine



Fig. 6.3 Postural changes

This patient has more severe ankylotic changes in the axial skeleton with more prominent limited movements in comparison with the patient in Fig. 6.1.

In advanced cases, there may be also advanced stoop with limited forward vision.

In Fig. 6.3a, there is a marked bending forward of the cervical spine, very limited lateral movements (Fig. 6.3b), and while in Fig. 6.1c the patient can bend forward further below the knees, in Fig. 6.3c, the patient can barely reach the level of his knees. The ST in this patient was positive (+1 cm).

Clinicians can use the BASMI form (Bath Ankylosing Spondylitis Metrology Index) to assess the spinal mobility in patients with AS. BASMI measures: (a) lateral lumbar flexion, (b) tragus-to-wall distance, (c) lumbar flexion (using the MST)



Fig. 6.4 Tragus-to-wall distance

In order to measure the tragus-to-wall distance, the patient stands in an upright position with heels and buttocks against the wall. The head is placed back as far as possible, keeping the chin in a horizontal plane. If the distance is >15 cm, then the test is considered positive. The tragus-to-wall distance shows the severity of the cervical spine ankylosis. Another alternative is to use the occiput-to-wall distance (Flesche test). This test is considered negative if the distance is 0 cm. In this figure two patients with AS and a positive tragus-to-wall distance test are shown.

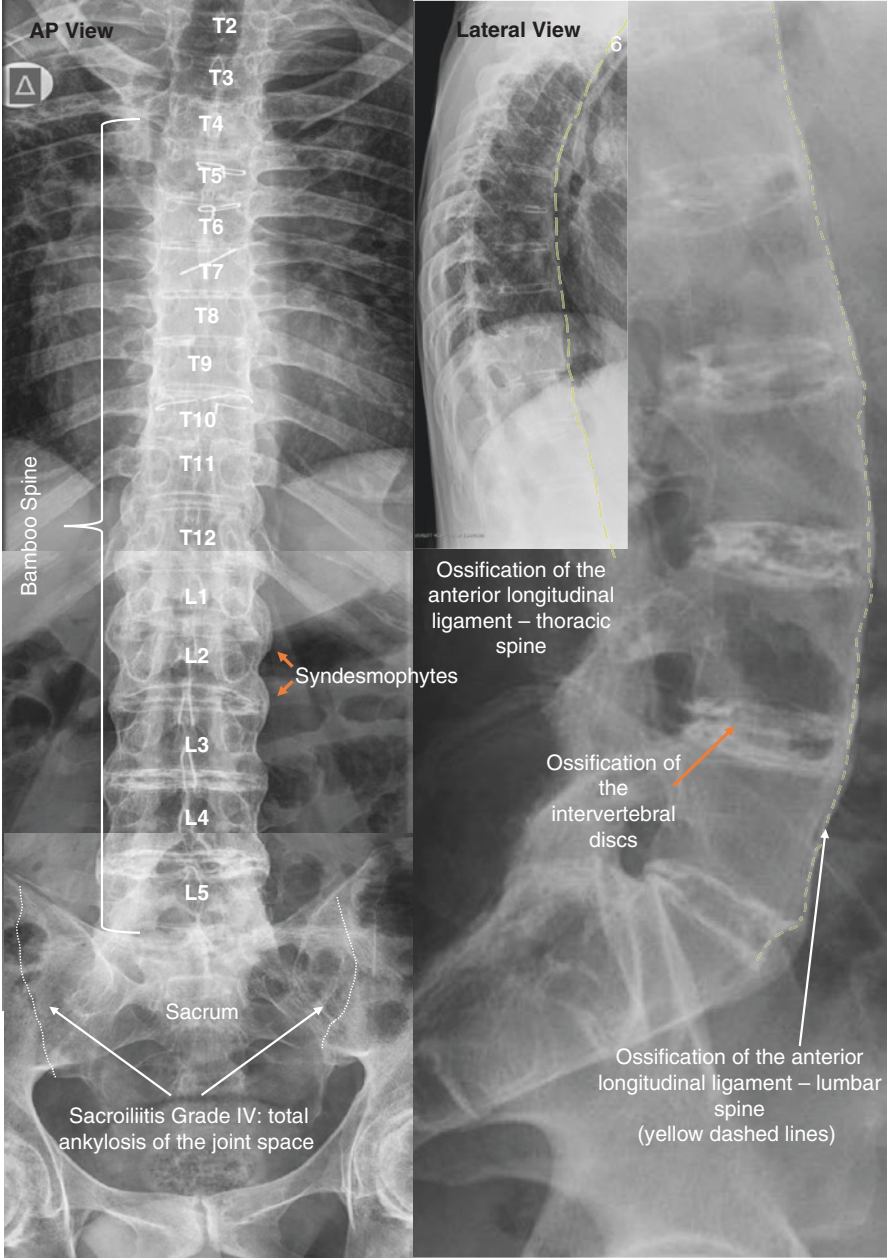


Fig. 6.5 In this figure different radiological features of AS are shown. Sacroiliitis is one of the hallmark features

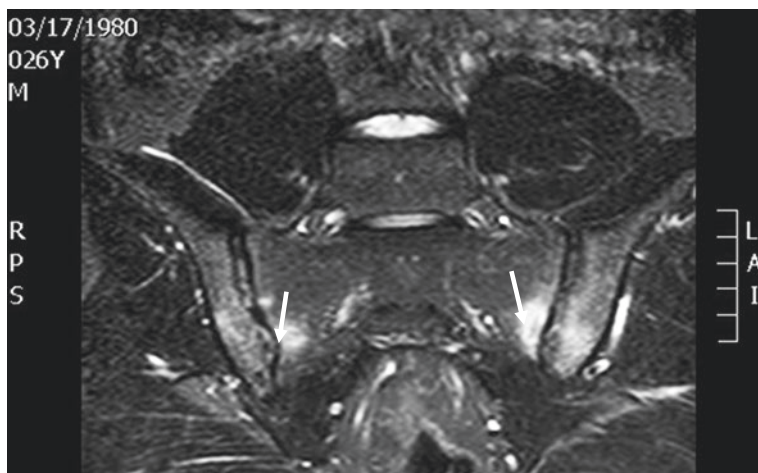


Fig. 6.6 Magnetic resonance imaging of the sacroiliac joints

This is a 28 years-old male who developed morning stiffness and low back pain. STIR sequences in coronal view revealed diffuse bone oedema with high signal of the SI joints bilaterally (white arrows), more prominent on the left side. This patient has been diagnosed with AS.

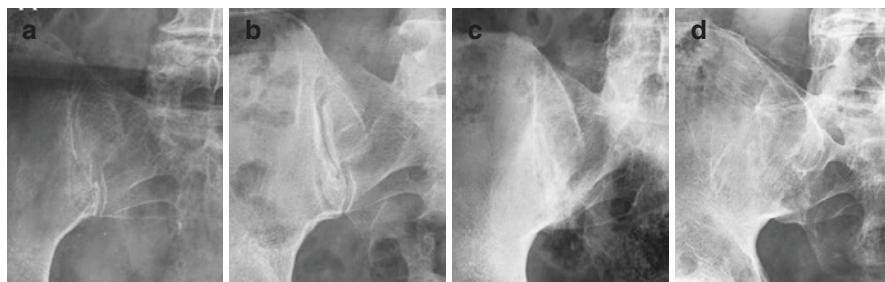


Fig. 6.7 Grading of radiographic sacroiliitis

The radiographic assessment of sacroiliitis can be done using the New York scoring method:

0 = no abnormalities.

1 = suspicious changes (no specific abnormalities – Fig. 6.7a).

2 = minimal sacroiliitis (some sclerosis and perhaps minimal erosions, there may be some joint space narrowing – Fig. 6.7b).

3 = moderate sacroiliitis (definite sclerosis on both sides of the joint, blurring and indistinct margins, and erosive changes with loss of joint space – Fig. 6.7c).

4 = complete fusion or ankylosis of the sacroiliac joint (without any residual sclerosis – Fig. 6.7d).

According to the modified New York criteria, at least grade 2 bilaterally or grade 3 or 4 unilaterally is necessary for the diagnosis of AS.

Fig. 6.9 Eye complications in ankylosing spondylitis

Figure 6.9a showing remnants (white arrows) of posterior iris synechiae after pupil dilation in a patient with recurrent anterior uveitis associated with AS.

Figure 6.9b shows another 70-year old patient with recurrent anterior uveitis and the formation of posterior synechiae.

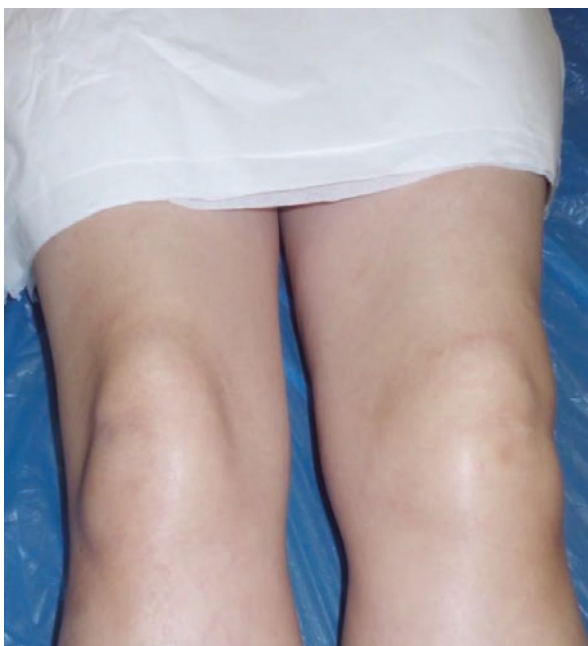


Fig. 6.8 Monoarthritis in ankylosing spondylitis

Monoarthritis is the inflammation of a single joint. It is usually caused by trauma, infection, or crystalline arthropathies. In AS, monoarthritis is a common manifestation, but the clinician should always think and rule out a septic arthritis case which can be devastating for the joint and the patient. To rule out septic arthritis, the clinician should perform a joint aspiration by inserting a needle into the affected joint and removing some fluid for microscopic analysis, gram stain and cultures. Inflammatory markers (e.g. CRP), fever and the clinical picture will guide the clinician for the correct decision. In this figure, the patient with AS has arthritis on her left knee (always compare the contralateral joint on examination).

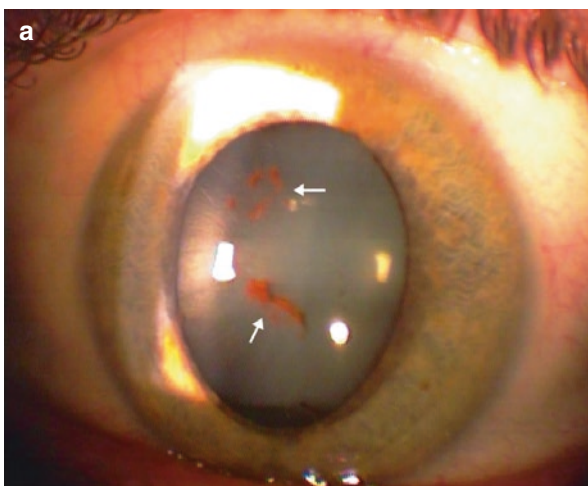
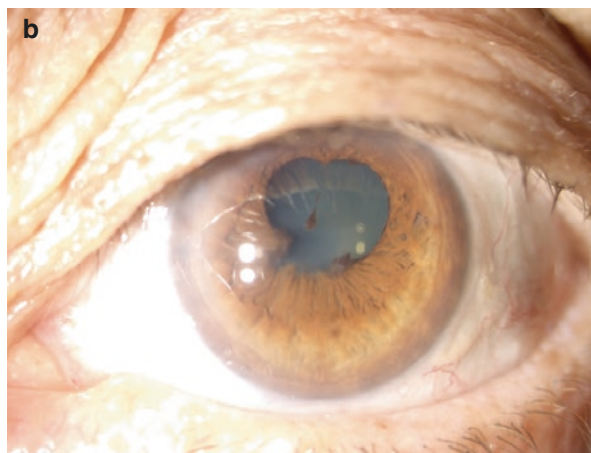


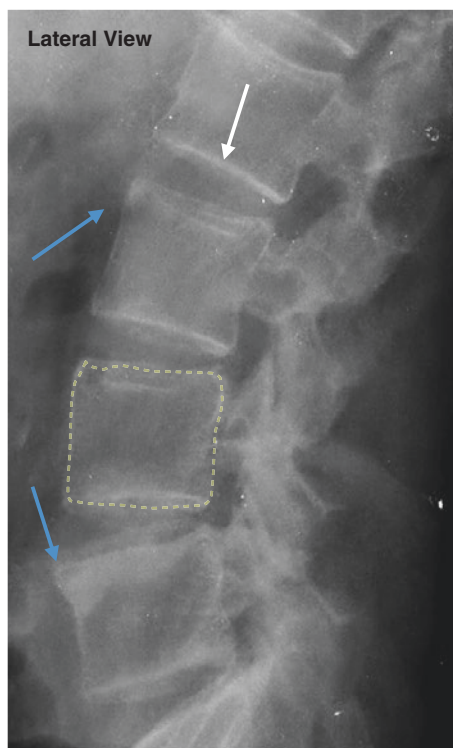
Fig. 6.9 (continued)**Fig. 6.10** Dactylitis

Dactylitis may be acute, with painful inflammatory changes, or chronic (as in Fig. 6.10a – 3rd toe), where the digit remains swollen despite the disappearance of acute inflammatory changes. Because of the diffuse swelling of the affected digit, it is referred to as “sausage digit” (see also the chapter of psoriatic arthritis).

Sometimes it can be confused with other conditions, such as nodal osteoarthritic changes (Fig. 6.10b – not uniformly swollen index finger in a patient with nodal osteoarthritis).

Fig. 6.11 Romanus lesion

Also known as the “shiny corner sign” (minimal variant), represents an early finding in AS but also in other inflammatory SpA as well. Another early finding is the squaring of the normally concave anterior border of the lumbar vertebrae. The originally described Romanus lesion is a sclerotic vertebral corner lesion accompanied by an end-plate erosion, which is confined to the anterior upper corner of the vertebra and most often seen in the lumbar spine. A faint sclerosis at the anterior vertebral corner, a minimal variant of the Romanus lesion, has been termed “shiny corner”. Romanus lesions and shiny corners tend to resolve over years and heal with syndesmophyte formation. This lateral view x-ray of the lumbar spine, reveals anterior corner Romanus lesions, best seen at the L5 and L3 (shiny corner) vertebral bodies (blue arrows). There is also squaring as well as sclerotic changes at the rims of the vertebral bodies (white arrow).

**Fig. 6.12** Avulsion fracture of the greater trochanter

Avulsion fractures develop when one part of the body is forcibly detached from another in response to trauma. Radiological avulsion fractures occur when a bony fragment is separated from the parent bone in response to forcible contraction of a ligament or tendon. This AS patient developed an avulsion fracture of the greater trochanter at the insertion of the gluteal muscles (blue circle). As a result, he was not able to extend and externally rotate the hip with ease. Other common sites that avulsion fractures can occur are (a) the ischial tuberosity at the insertion of the adductor magnus muscle of the hamstring (green line), (b) the anterior inferior iliac spine at the insertion of the rectus femoris muscle (red line), and, (c) the anterior superior iliac spine at the sartorius muscle insertion (yellow line).

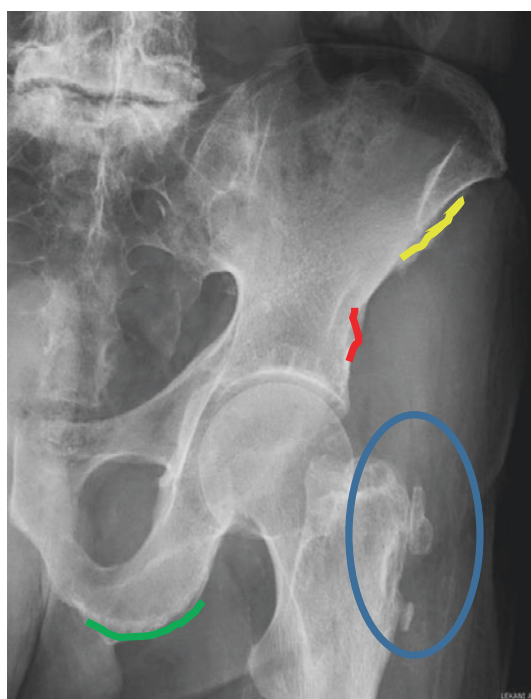


Fig. 6.13 Dagger sign and jug-handle sign
The dagger sign is a single central radiodense line on anteroposterior (AP) radiographs of the spine. It is a sign of ossification of supraspinous and interspinous ligaments (yellow arrows). The jug-handle sign is best seen in the formed syndesmophytes of L1–L2 vertebral bodies (white arrows). Usually, it is bilateral in AS but could be unilateral in psoriatic arthritis.

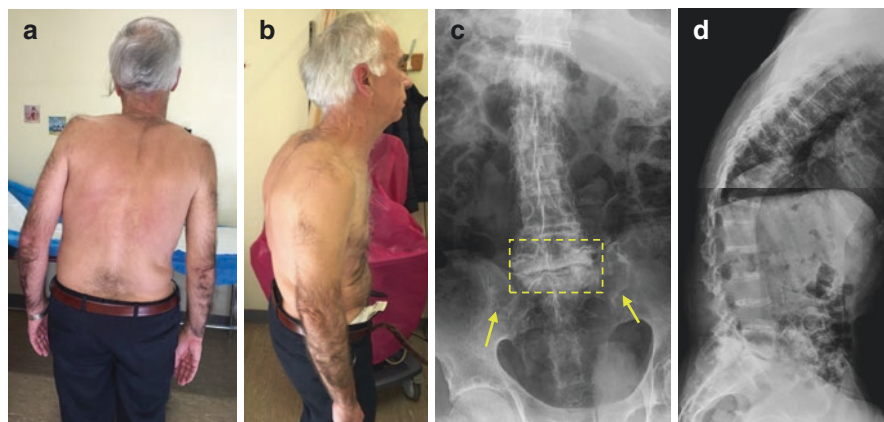
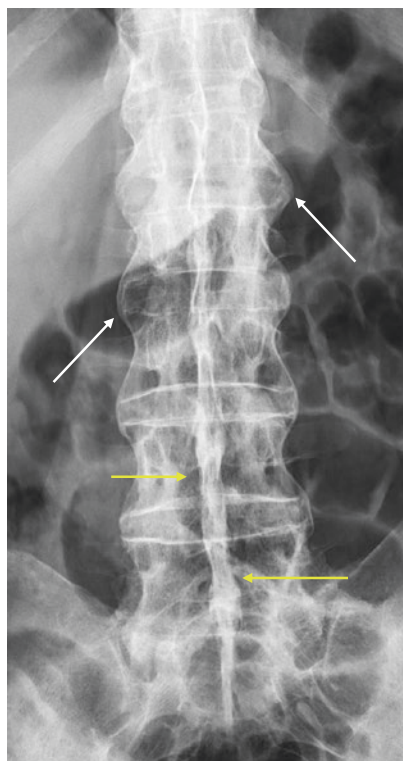


Fig. 6.14 A patient who had never received treatment for ankylosing spondylitis
This 70-year-old patient had never received treatment for his AS. He attended the clinic due to an excruciating pain on his lower back. Clinical examination revealed severe kyphoscoliosis affecting the thoracic and lumbar spine as well as a bending forward position of the cervical spine (Fig. 6.14a, b). The x-ray of the lumbar spine revealed that the patient was suffering from spondylitis in L5–S1 (Fig. 6.14c – yellow dashed rectangle).
Also, there is a significant kyphoscoliosis (Fig. 6.14c, d) in the lumbar and thoracic spine. Extensive ossification of the intervertebral discs as well as the supraspinous ligaments. Grade IV sacroiliitis bilaterally (yellow arrows) and subchondral cysts with calcification of the acetabular margins.

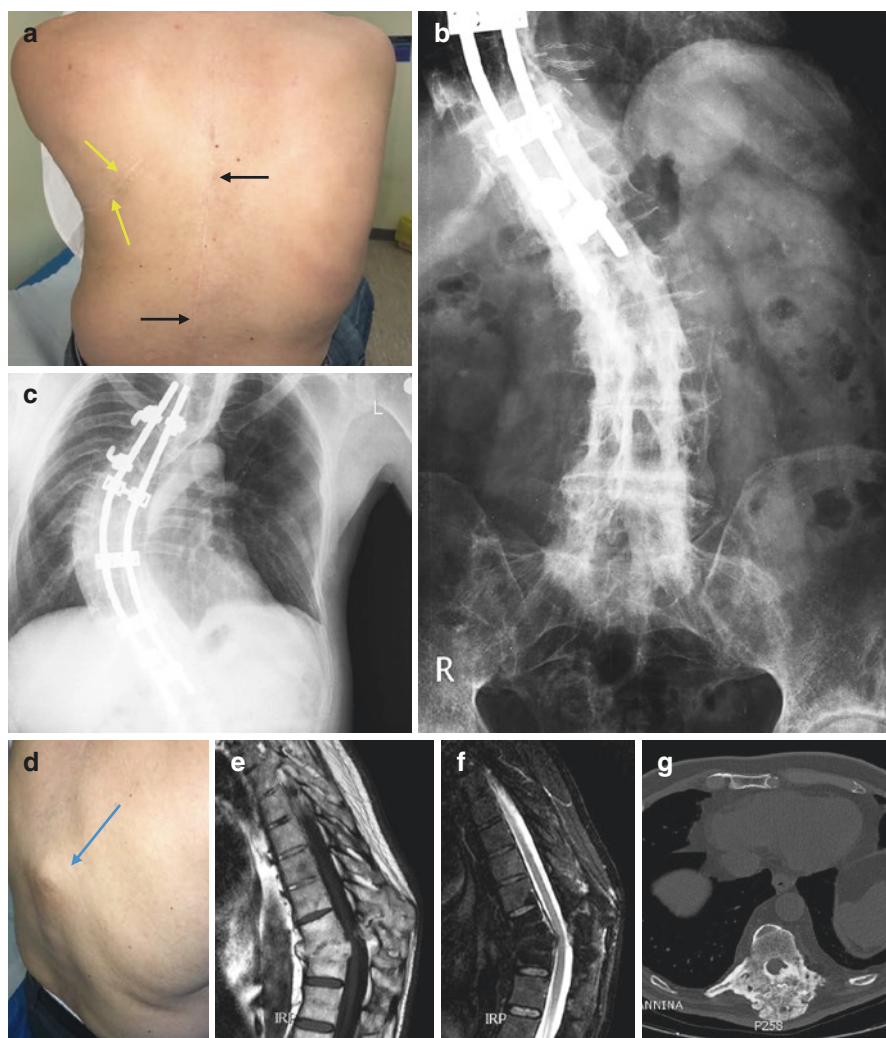


Fig. 6.15 Miscellaneous findings in ankylosing spondylitis patients

Patients with AS can develop different deformities of the axial skeleton. In Fig. 6.15a–c, the patient had an orthotic surgery of his spine due to severe scoliosis (note the long longitudinal scars from the operation – black arrows). The surgeons had to remove ribs from the right side of the rib cage in order to complete the operation (yellow arrows).

In Fig. 6.15d, there is a protrusion (gibbus) at the level of T11–T12 due to a fracture of the ankylosed spine (blue arrow). In Fig. 6.15e, the fracture as seen on MRI, and in Fig. 6.15f the stenosis of the spinal canal. In Fig. 6.15g stenosis of the spinal canal and the fracture as seen on a transverse CT plane.

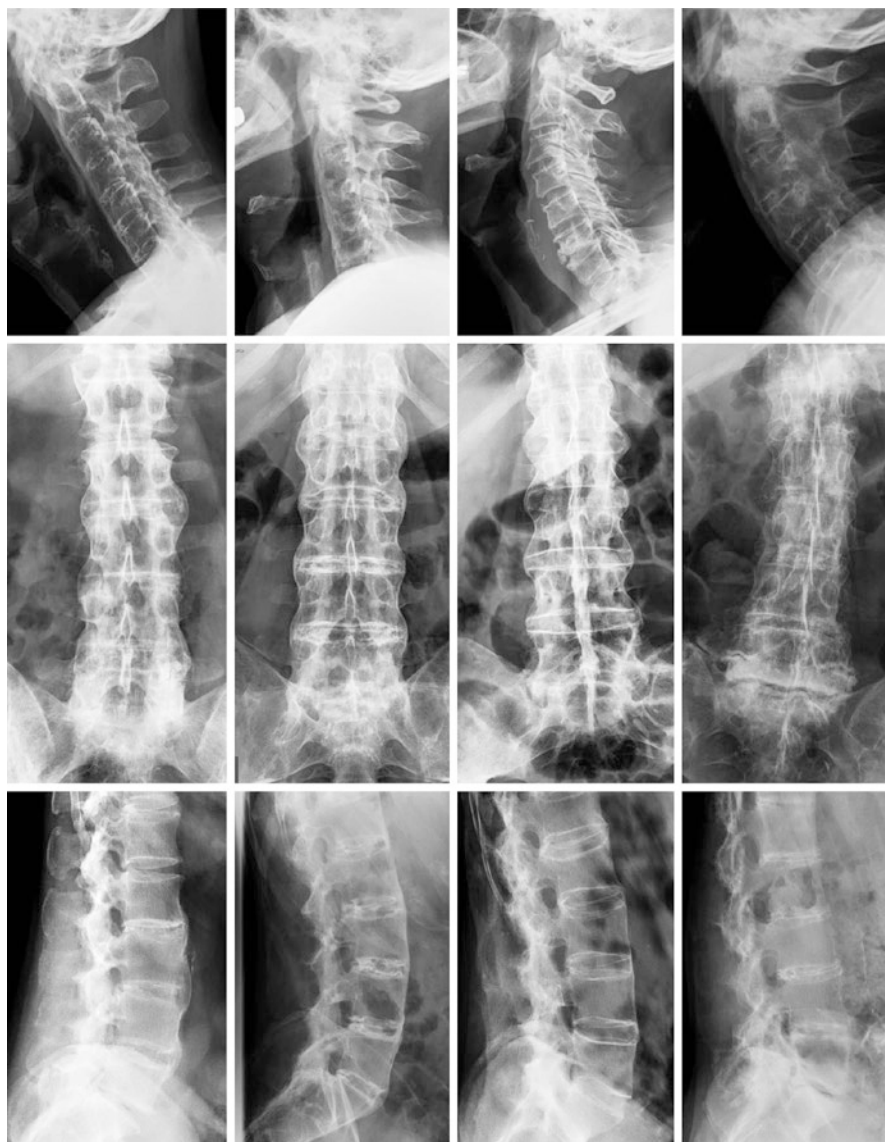


Fig. 6.16 X-rays of different patients with ankylosing spondylitis on different stages
First row: cervical spine deformities in lateral view.
Second row: lumbar spine deformities in AP view.
Third row: lumbar spine deformities in lateral view.

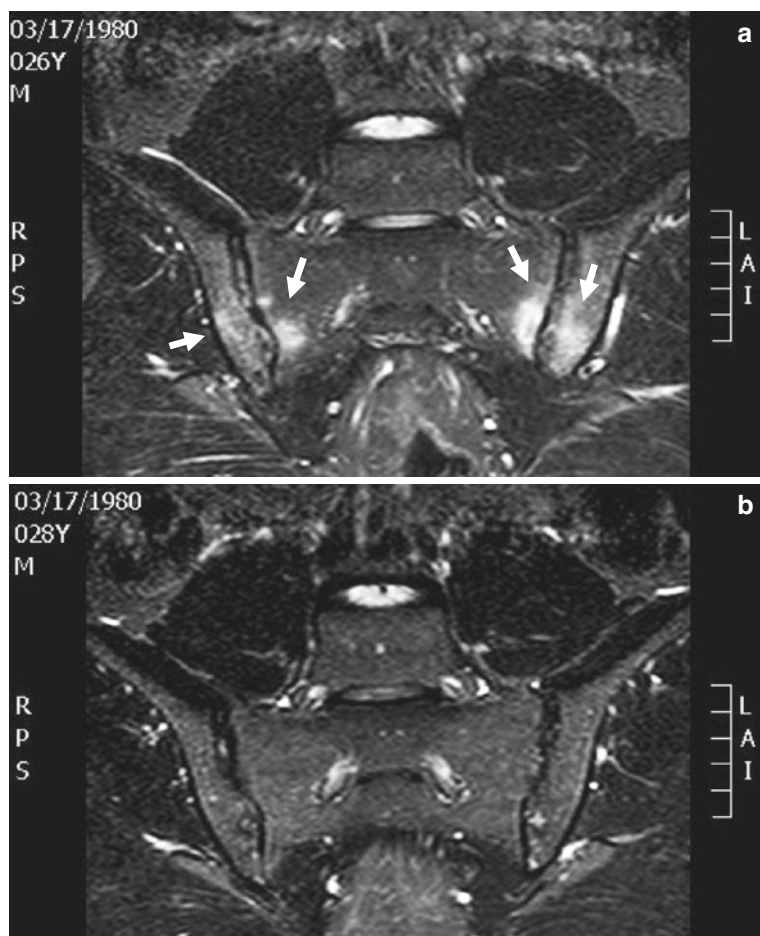


Fig. 6.17 Magnetic resonance imaging of the sacroiliac joints in a patient after treatment with TNFi

This is a 28 years-old male who developed morning stiffness and low back pain. STIR sequences in coronal view revealed diffuse bone oedema with high signal of the SI joints bilaterally (white arrows), more prominent on the left side (Fig. 6.17a). This patient has been diagnosed with AS. In Fig. 6.17b, the same patient after 2 years of treatment with Infliximab. Note the complete reversal of the bone oedema. The patient was in clinical remission.

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Chapter 7

Systemic Lupus Erythematosus



7.1 Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease affecting multiple organ systems. The course of the disease is unpredictable with mild to life-threatening complications. Circulating autoantibodies directed against cell nuclear components is the main laboratory characteristic. As in other autoimmune diseases, the direct (health care costs) and indirect (productivity loss) socioeconomic costs of the disease are of major significance with an average annual direct medical cost to range approximately between 4000–10,000 euros (mild/severe cases respectively). Hippocrates was the first who described cutaneous ulcerations consistent with SLE. The word “lupus” comes from the Latin, which means “wolf”. It is attributed to the thirteenth century physician Rogerius who used it to describe erosive facial lesions that were reminiscent of a wolf’s bite. In 1872, cutaneous lupus (CL) was identified as a distinct form of SLE. In 1948 the lupus erythematosus cell (LE) was discovered by the American clinical haematologists Malcolm Hargraves and Robert Morton and it allowed the diagnosis of individuals with different forms of the disease.

7.2 Aetiology and Pathogenesis

The aetiology of SLE is unknown, but genetic, environmental and hormonal factors may predispose to disease manifestation and expression. These factors lead to an irreversible breakdown of immunological tolerance manifested by aberrant immune response against endogenous cellular and circulating self-antigens. Siblings of patients with SLE are 30 times more likely to present SLE compared to people without an affected sibling. The risk of SLE may also be influenced by epigenetic effects such as DNA methylation. Among environmental factors, ultraviolet light, demethylating drugs, infections, hydralazine, and procainamide have been reported. Oestrogen or prolactin can lead to an immune phenotype with B-cell autoreactivity. Regarding disease pathophysiology, a large number of cells and molecules that participate in apoptosis, innate and adaptive immune responses are involved.

7.3 Epidemiology

The prevalence of SLE ranges from 20 to 150 cases per 100,000 persons, although there are major variances in different populations. The variability may result from differences in methods of case ascertain and socioeconomic causes. The incidence of SLE varies according to the characteristics of the population studied (age, sex, race, ethnicity etc.). In Europe, the annual incidence ranges from 3.3–4.8 cases per 100,000 persons, whereas in the United States of America the annual incidence

ranges from 2.0–7.6. A female to male ratio is about 9:1 but there are studies showing a female preponderance reaching to 15:1. Peak SLE incidence rates occur during the early reproductive years in women (young women between the late teens and early 40's).

7.4 Classification Criteria

The classification criteria for SLE have been developed by the American College of Rheumatology (ACR) in 1971 and have been revised in 1982 and 1997. The criteria have been developed and validated in patients with longstanding and established disease and may exclude patients with early or limited disease. However, despite the fact that the criteria have been developed for classification purposes, they often are used by physicians for the diagnosis of SLE, and this could lead to errors and caveats. The classification criteria include: (1) malar rash, (2) discoid rash, (3) photosensitivity, (4) oral or nasopharyngeal ulcers, (5) non-erosive arthritis, (6) serositis (pleurisy, pericarditis, peritonitis), (7) renal manifestations (persistent proteinuria >0.5 gr or cellular casts), (8) neurological manifestations (psychosis, seizures), (9). haematological manifestations (haemolytic anaemia, lymphopenia, thrombocytopenia), (10) immunological manifestations [anti-double-stranded(ds)-DNA, anti-Sm, presence of antiphospholipid antibodies (APL) – anticardiolipin antibodies (aCL)/lupus anticoagulant (LA)/false positive serological test for syphilis], (11) Positive anti-nuclear antibodies (ANA). The patient is classified with SLE using the ACR criteria if four or more of the above manifestations are present, either serially or simultaneously, during any interval of observations.

7.5 Signs and Symptoms

Not all the patients will have the same course of the disease. Symptoms may vary from person to person but also even if they have the same symptomatology they may have different evolution.

Constitutional symptoms: patients with SLE often present with malaise, arthralgias, myalgias, weakness, headache, low grade fever or high spiking fever.

Musculoskeletal involvement is a very common feature of SLE. Arthralgia occurs in about 90% and muscle involvement in 30–50% of all patients with SLE. Articular involvement may have clinical features seen in rheumatoid arthritis (RA) but there are differences that can distinguish those two clinical entities. Arthritis, has the same character as in RA but synovial effusions are uncommon, the deformities are not usually associated with synovial hypertrophy or bony erosions and the deformities are in general reducible (Jaccoud's arthropathy). Muscle tenderness and diffuse myalgias are common during disease exacerbations. Inflammatory myositis affecting the proximal muscles has been also described in about 5–10%.

Skin and mucosal involvement has some typical features for the disease with a wide variety of disorders. Malar rash or butterfly rash is the first criterion of the ACR. It is an erythematous rash over the cheeks and nasal bridge that typically spares the nasolabial folds. Exposure to ultraviolet light may cause a macular or a diffuse erythematous rash in sun-exposed areas (usually affects the face, arms, and hands). Discoid rashes appear in chronic skin disease known as chronic cutaneous lupus erythematosus (CCLE) and are coin-shaped erythematous plaques of varying size. Alopecia appears in about 45% of patients during the course of the disease. Raynaud's phenomenon (RP), an abnormal vasoconstriction of digital arteries and cutaneous arterioles, is reversible and may be exaggerated in cold temperatures or emotional stress. Cutaneous vasculitis may present in several forms such as punctate lesions, palpable purpura, urticaria, ulcers, erythematous plaques or macules and even necrosis of the affected skin. Periungual telangiectasias is thought to be an indicator for systemic disease activity. Livedo reticularis (LR) is found frequently on the lower extremities and is a cutaneous vascular reaction that appears as a mottled reticular pattern with a violaceous discoloration. Atrophie blanche is a particular type of scar arising on the lower leg that occurs after a skin injury when the blood supply is poor. Oral ulcers, which may be painless or painful, is another finding in SLE (palatal ulcers are most specific for the disease).

Renal involvement is one of the most serious manifestations of SLE and approximately 40–70% of patients will present lupus nephritis (LN) at some stage of their disease. There are different pathological classes of LN, but diffuse proliferative (Class IV) has the worst prognosis and may lead to end stage renal disease at 5 years in up to 50% of patients. The World Health Organization (WHO) classification system of lupus nephritis includes also: minimal change (Class I), mesangial (Class II), focal proliferative (Class III), membranous (Class V), advanced sclerosis (Class VI).

Cardiac involvement is common (>50%). Pericarditis is the most common cardiovascular manifestation of SLE, and it appears more frequently at SLE onset or during SLE relapses. Myocarditis and endocarditis (Libman-Sacks) have been probably underestimated due to the subclinical nature of the symptoms.

Pulmonary involvement in SLE has a subclinical form most of the times. Small to moderate pleural effusions are not uncommon. Lupus pneumonitis with inflammatory infiltration in the alveolar septae is another finding in SLE patients but in general, parenchymal alterations, attributable to SLE in sine, have been described in a minority of patients (18%). Pulmonary haemorrhage is a rare but potentially catastrophic manifestation of SLE. Another lung manifestation of SLE is the "shrinking lung syndrome (SLS)". It is thought to be secondary to diaphragmatic dysfunction due to respiratory muscle weakness, or pleural causes or due to parenchymal disease.

Haematological abnormalities are common findings in patients with SLE. It is important to distinguish haematological abnormalities as either manifestation of SLE, consequence of SLE treatment or as part of another blood dyscrasia. Neutropenia, lymphopenia, auto-immune haemolytic anaemia (AIHA), and thrombocytopenia are not uncommon findings in SLE patients.

Nervous system involvement: a new headache that does not respond to analgesics may sometimes herald severe neurological disease manifestations with altered mental status, meningitis, psychosis, seizures, myelitis or cognitive dysfunction. Cranial and peripheral nerves may also be affected.

7.6 Differential Diagnosis

The differential diagnosis of SLE includes patients with other autoimmune rheumatic diseases such as systemic vasculitis, mixed connective tissue disease (MCTD), or chronic infections and conditions causing positive ANAs and or cytopenias. These, include leishmaniasis, hepatitis B and C, cirrhosis and malignancies. Thus, a detailed past medical history, complete physical examination, as well as, appropriate laboratory and imaging tests will help physicians to differentiate SLE from the above conditions.

7.7 Diagnostic Modalities

Laboratory: full blood count (FBC) with differential is always important to be tested since SLE causes cytopenias. To this end, it is important to check for haemolytic anaemia with Coomb's test.

Erythrocyte sedimentation rate (ESR) is a sensitive but not specific and slow indicator of activity in SLE. C-reactive protein (CRP) can be used to distinguish bacterial infections (high CRP) from active SLE (usually low CRP). Nevertheless, lupus serositis and arthritis can lead to high CRP values.

Antinuclear antibodies (ANA) are present in almost all patients with SLE but when a patient has a positive ANA titre does not mean that has SLE. An ANA titre higher than 1/160 is considered an important index in patients with high probability for SLE.

Double-stranded-DNA (ds-DNA) are associated with systemic lupus and nephritis.

Antihistone antibodies might reflect disease activity, but are not specific for SLE. Also, they cannot distinguish drug induced SLE from idiopathic.

Extractable nuclear antibodies (ENA) such as Ro (SS-A) and La (SS-B) are found in SLE and Sjögren's syndrome (SS). Anti-Ro60 antibodies predominate in SLE whereas anti-Ro52 in SS. Anti-Ro is associated with cutaneous lupus erythematosus (CLE), and with congenital heart block (CHB). High titre anti-Sm is highly SLE-specific and are rarely found without anti-RNP (ribonucleoprotein) antibodies.

Ribosomal P antibodies are associated with neuropsychiatric SLE.

Antiphospholipid (APL) antibodies such as ACL and anti- β 2-glycoprotein I (β 2-GPI) antibodies with LA testing can be a risk factor for thrombosis.

Complement levels are usually normal, but low C3 and C4 can indicate activity of the disease.

Lupus erythematosus cell (LE) was first described in the bone marrow preparations of patients with lupus erythematosus and was later shown that the cell can be equally demonstrated in peripheral blood preparations. Its absence in the appropriate clinical context does not exclude the diagnosis. The LE consists of a leucocyte (neutrophil/macrophage), whose cytoplasm contains a large, spherical and homogeneous body, which stains pale purple with Romanowsky stains and has phagocytised the denatures nuclear material of another cell.

7.8 Management

Medical Treatment: the current treatment approach includes antimalarial drugs, steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), and immunosuppressive drugs, including cyclophosphamide (CP), azathioprine (AZA), mycophenolate mofetil (MMF).

Antimalarial drugs remain the first-line treatment for patients with mild SLE. NSAIDs can be used in parallel with antimalarials. Hydroxychloroquine (HCQ) is the most used antimalarial drug.

Corticosteroids (CS) are the mainstay of treatment in SLE patients, especially in disease flares.

CP plus CS are the mainstay in LN. Because of the side effects of CP, other immunosuppressive agents are preferred for maintaining remission, such as AZA and MMF.

MMF can be used as induction therapy for LN with the same or even better results than CP but also as maintenance therapy.

AZA can be used as a CS-sparing agent, but usually is not well-tolerated by the patients (gastrointestinal tract side-effects, liver dysfunction and leukopenia).

Other immune cell-targeted therapies with agents that target B-cells (rituximab, belimumab) are used.

Lifestyle: patients suffering from SLE should avoid sun exposure and use the appropriate prophylactic measures such as sunscreen and clothing on the sun-exposed areas of the body. Reducing stress can lead to less disease flares. Also, extra rest during a flare is indicated. Due to recent evidence of increased risk of myocardial infarction in SLE patients a low-fat, low-cholesterol diet is suggested in conjunction with exercise, avoiding smoke and maintaining a healthy weight.



Fig. 7.1 Different skin manifestations in systemic lupus erythematosus

Most patients with SLE will develop skin rashes and it can be the first sign that will eventually lead the patient to a primary care physician and later to a dermatologist or a rheumatologist. Figure 7.1a–d show four different patients with the “classic” malar or the so-called butterfly rash on their face. The malar rash of SLE has the shape of a butterfly and involves the bridge of the nose but it spares the nasolabial folds, which contributes to its characteristic appearance. Another characteristic of the malar rash is that resolves without scarring but it may result in persistent telangiectasias (*see* Fig. 7.2a, b). These typical skin rashes can be induced or aggravated by exposure to ultraviolet radiation and are localised in sun-exposed sites such as the face, but other sites are not uncommon. Patients with SLE may also develop other types of skin rashes such as annular lesions. In Fig. 7.1c and e, typical skin annular lesions on the V of the chest and upper back respectively, are depicted. Those lesions, which are usually found in subacute cutaneous lupus erythematosus (SCLE), are polycyclic with an erythematous scaling border with central clearing and usually tend to coalesce. Figure 7.1f shows the patient from Fig. 7.1d after treatment. Note that the skin manifestations have disappeared.

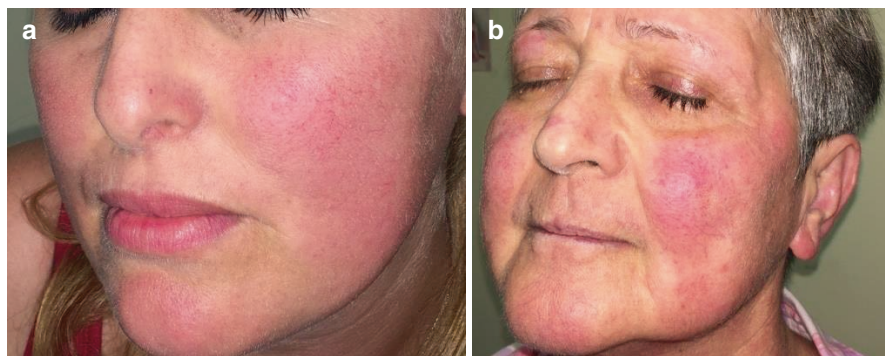


Fig. 7.2 Face telangiectasia

As described in Fig. 7.1, the malar rash can resolve without scarring, but it may result in persistent telangiectasia and a mild facial erythema as shown in these SLE patients (Fig. 7.2a, b).



Fig. 7.3 Skin manifestations in subacute cutaneous lupus erythematosus

SCLE consists of non-scarring papulosquamous or annular skin lesions which occur in a characteristic photo-distribution. Figure 7.3a, b show a patient with annular SCLE. Note the polycyclic array resulting from the confluence of the individual annular lesions in Fig. 7.3b. Figure 7.3c, d show the papulosquamous SCLE form on the mid- and upper back and on the extensor surface of the antibrachium respectively. Note the superficial scale and the tendency for the individual lesions to merge into a retiform pattern.

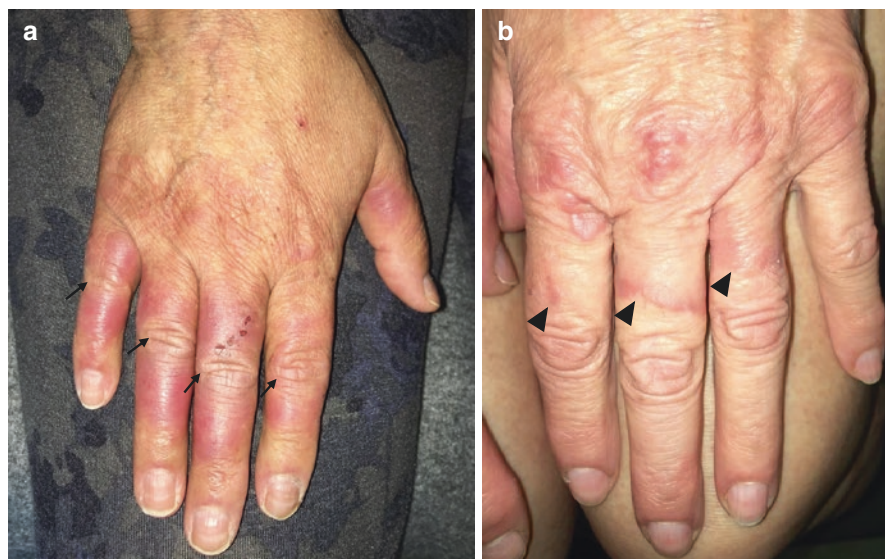


Fig. 7.4 “Inverse” Gottron’s papules or inverse Gottron’s sign

As it will be described in the chapter about Dermatomyositis, Gottron’s papules are erythematous to violaceous and sometimes scaly bumps that erupt on any of the metacarpophalangeal (MCP) or interphalangeal (IP) joints. Lupus patients, in the acute set, present a similar sign, but it tends to spare the IP joints and it can be found as an erythema over the extensor aspect of the wrists that becomes confluent over the dorsal aspect of the hand and interphalangeal areas.

Figure 7.4a shows the hand of a lupus patient with the “inverse Gottron’s sign” which affects the phalangeal skin but spares the knuckles (black arrows).

In Fig. 7.4b another patient with a mild form of the “inverse Gottron’s sign”. Note the mild erythema in the interphalangeal areas (black arrowheads).

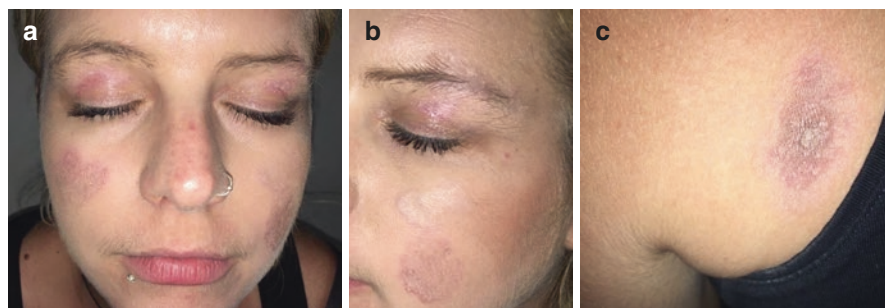


Fig. 7.5 Chronic cutaneous lupus erythematosus – discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common form of CCLE. Lesions of this type may begin as flat or slightly elevated, well-demarcated, red-purple macules or papules with a scaly surface. The term “discoid” comes from the coin-shaped appearance of the lesions. These coin-shaped lesions can enlarge and merge to form even larger, confluent plaques that can be disfiguring (Fig. 7.5a). When these lesions develop over hairy areas they can cause permanent hair loss (Fig. 7.5b – distal 1/3 of left eyebrow). Skin lesions in lupus cause distress in patients, especially at younger ages, as in this 27-year-old patient who tries to hide the lesions with make-up even at the back of her left shoulder (Fig. 7.5c).



Fig. 7.6 Discoid lupus erythematosus

Erythema and hyperpigmentation are present during the initial phase of DLE lesions but on later stages the skin becomes hypopigmented. Perioral involvement is not uncommon and can produce loss of hair follicles and a central atrophic scarring with skin depigmentation which is highly characteristic, as seen in this patient in Fig. 7.6.



Fig. 7.7 Perioral pitted scarring in discoid lupus erythematosus

Perioral pitted scarring resulting from prior DLE involvement (Fig. 7.7). This is an acneiform pattern of pitted scarring in contrast with the atrophic scarring seen in Fig. 7.6.

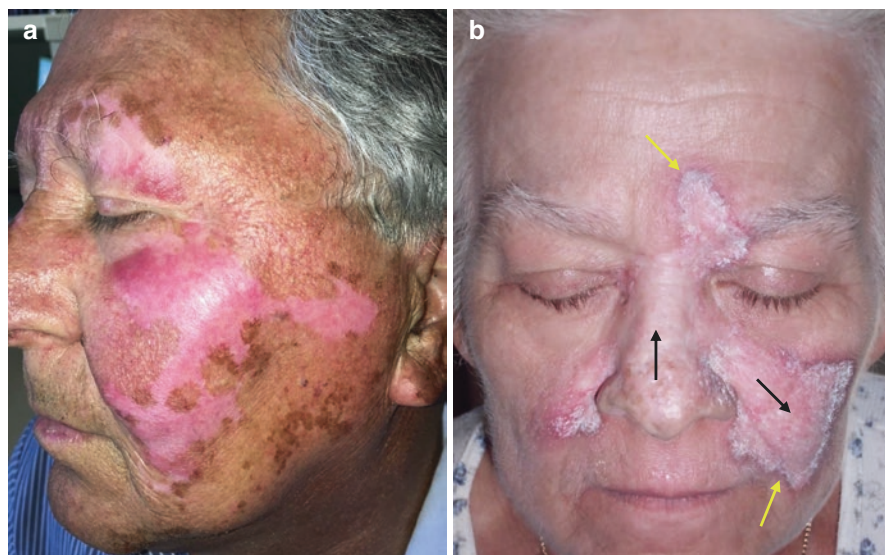


Fig. 7.8 Chronic cutaneous lupus erythematosus – extensive facial discoid lupus erythematosus lesions

These are two characteristic examples of different patients with chronic DLE lesions. Figure 7.8a depicts a patient with chronic facial lesions that led to skin atrophy and marked confluent areas of depigmentation without scarring, whereas in Fig. 7.8b there is significant scarring. The characteristic pattern of hyperpigmentation at the active border (yellow arrows) and hypopigmentation at the inactive center (black arrows) is especially evident in black patients but severe lesions can be noticed in whites as well.

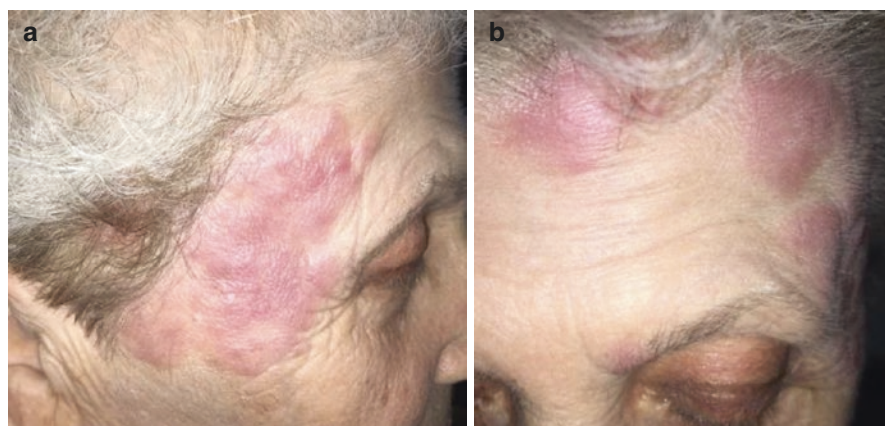


Fig. 7.9 Lupus erythematosus tumidus

Lupus erythematosus tumidus (LET) is a rare subset of CCLE and is characterised by erythematous, non-scarring, succulent, oedematous plaques in sun-exposed areas. The appearance is urticarial-like. In Fig. 7.9a and b, such lesions are evident bilaterally in a patient suffering from CCLE.

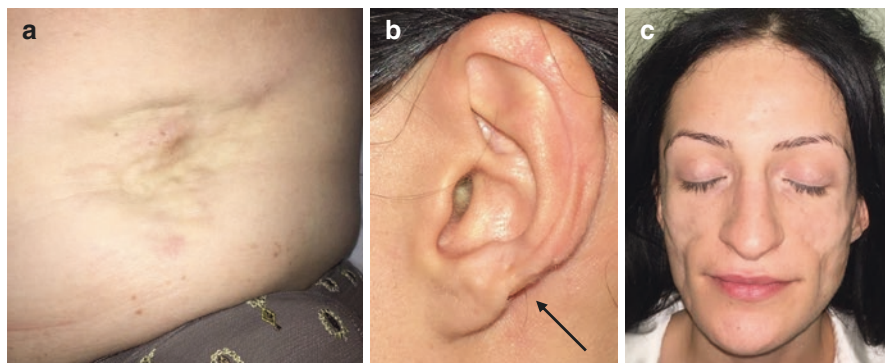


Fig. 7.10 Lupus erythematosus profundus/lupus erythematosus panniculitis

This not so common form of SLE may occur in the absence of systemic disease. In the past, it was called with the eponym Kaposi-Irgang disease. This is also a subset of CCLE and it is characterised by inflammatory lesions in the lower dermis and subcutaneous tissue. At the beginning, the lesions consist of deep, firm nodules. The overlying skin progressively becomes attached to the firm, subcutaneous nodular lesions and is drawn inward to produce deep depressions as seen in Fig. 7.10a or resulting in a soft flopped tissue as it is seen in Fig. 7.10b (black arrow). In Fig. 7.10c, confluent lesions of the face simulate the appearance of lipoatrophy.



Fig. 7.11 Rheumatoid pattern arthropathy in systemic lupus erythematosus

Joint involvement in SLE is a common presenting feature. The clinical presentation may be mimicking an acute presentation of RA and may be difficult to differentiate between the two diseases. There is usually no evidence of erosive changes on radiographs in contrast to RA. In Fig. 7.11 note the symmetrical swelling of the proximal interphalangeal (PIP) and MCP joints.

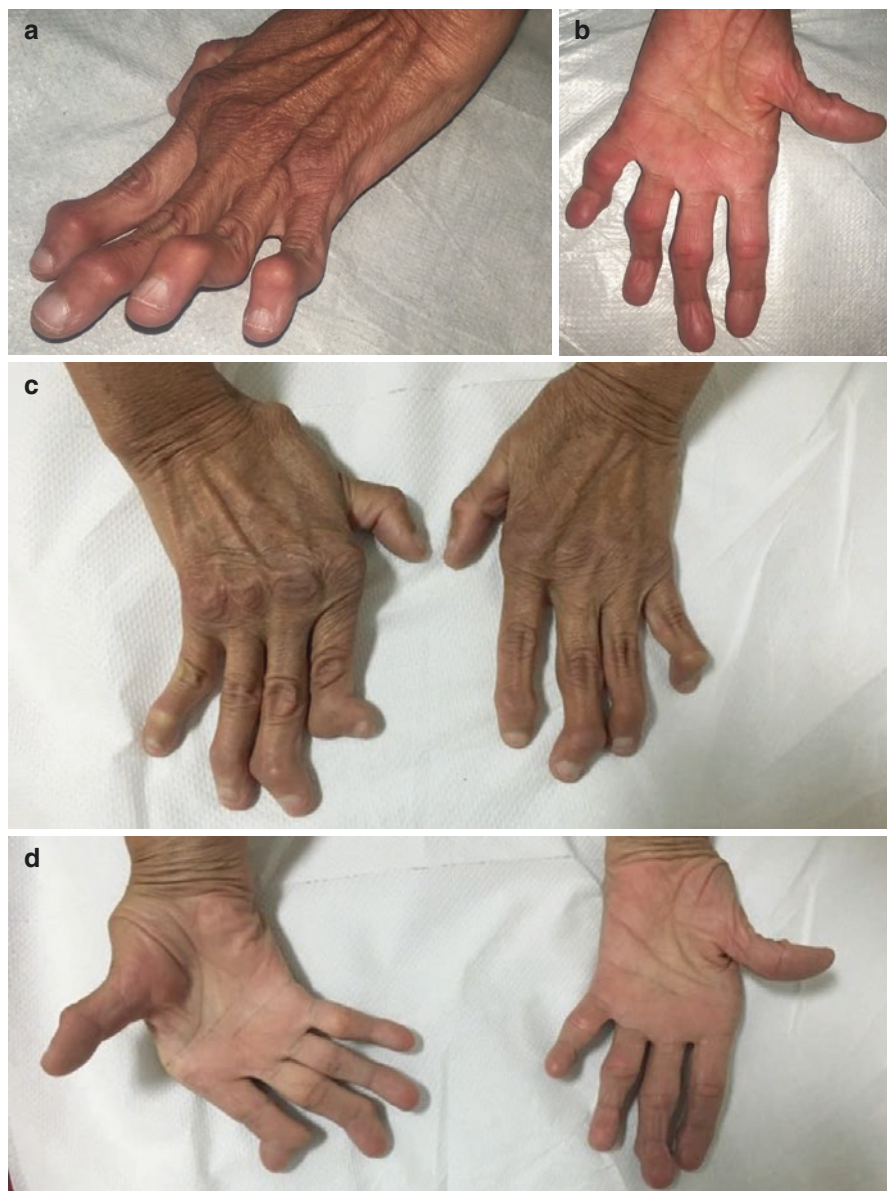


Fig. 7.12 Jaccoud's arthropathy

As mentioned above, the arthritis is non-erosive, but ligamentous laxity can result in deformities similar to those seen in RA patients. The difference is that these deformities are reducible. In Fig. 7.12a–d there are swan neck deformities but these are fully reducible and the patient is still able to make a complete fist. This deformity is a result of ligamentous laxity rather than joint subluxation. You can also notice the interosseous muscle atrophy (volar aspect of the hand) and the thenar eminence atrophy (palmar aspect).



Fig. 7.13 Hand x-ray in systemic lupus erythematosus

A hands x-ray of an SLE patient. Note that there are no erosive changes, but only joint space narrowing in the MCPs and bone deformities more prominent in the right hand. A hand x-ray may be similar between SLE and RA patients. In such cases, other diagnostic criteria for SLE will help determine which entity is predominant. Ulnar drift, swan neck and boutonniere deformities as well as juxta-articular osteoporosis are some characteristics of the disease. On the other hand, erosive findings would be characteristic of RA.



Fig. 7.14 Splinter haemorrhages

Splinter haemorrhages are not specific to any particular condition, and can be associated with antiphospholipid syndrome (APS) and SLE but also other connective tissue diseases, malignancies, infections (infective endocarditis) and trauma. Splinter haemorrhages are linear reddish-brown streaks noted on the nail plates. This patient has been diagnosed with SLE and has no history of trauma.



Fig. 7.15 Subungual haemorrhages in systemic lupus erythematosus
Splinter haemorrhages in a patient with a clinically active SLE. Even if this is not a specific finding for SLE, it is thought to be a poor prognostic factor and is associated with vasculitis.



Fig. 7.16 Common warts of the hands and feet in systemic lupus erythematosus
Immunosuppressant and steroid therapy as well as possible immunological defects among patients with SLE increase the risk of human papillomavirus (HPV) infections. The prevalence of common warts in SLE is increased when compared with other rheumatic conditions. Common warts, are elevated, hyperkeratotic papules with a rough surface. Small, clotted blood vessels may be seen at the surface (insert picture in Fig. 7.16b in more detail). They may be solitary or multiple. They tend to resolve spontaneously within 2 or 3 years in the general population and are not usually painful. In SLE patients due to immunosuppression usually last longer. This SLE patient was on long-term CS use and had multiple lesions on both hands and feet.



Fig. 7.16 (continued)

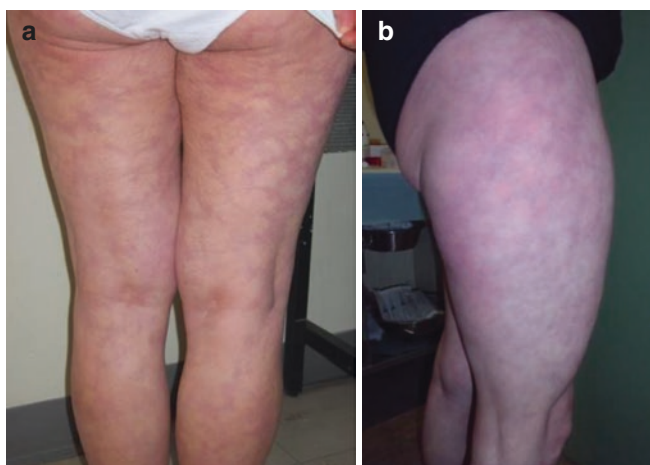


Fig. 7.17 Livedo reticularis in systemic lupus erythematosus

LR is not a specific finding for SLE, but is commonly seen in lupus patients and is due to spasm of the dermal ascending arterioles. It is characterised by the appearance of a reticulate pattern of unbroken circles/hexagons in the superficial vascular networks of the skin. The condition may be normal or may be related to severe underlying pathology. It may be aggravated by exposure to cold. It has been recognised that LR can be a manifestation of the presence of APL antibodies in patients with SLE. In addition to the livedo pattern on the skin, these patients may demonstrate acrocyanosis, small vessel infarction (predominantly on the lower extremities) producing atrophic blanche-like lesions. Livedo usually appears as a broad-based, interrupted pattern, in contrast to the thin, well connected livedo that may be seen in normal individuals. Figure 7.17a–d depict different patterns of LR in patients with SLE.

Figure 7.17e shows a patient with erythema ab igne. This condition should be in the differential diagnosis of the physician because it highly resembles livedo reticularis. Erythema ab igne is a skin reaction to chronic exposure to heat, especially in the elderly who sit close to open fires or electric heaters.

Finally, livedo racemosa (Fig. 7.17f, g) differs from livedo reticularis in appearance. Livedo racemosa appears as an asymmetric irregular reticulate pattern of broken circles and usually does not develop in otherwise healthy people. Almost always, it signifies a pathological process.

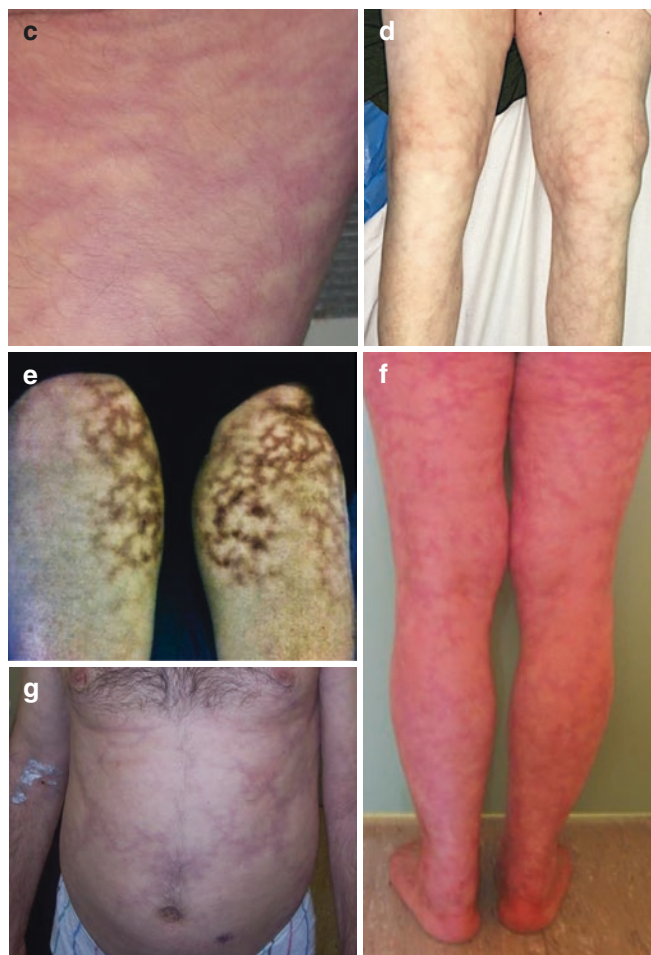
Fig. 7.17 (continued)



Fig. 7.18 Thrombosis in antiphospholipid syndrome

APS is an immune mediated systemic disease characterised by recurrent thrombotic events and pregnancy complications. It can be categorised as primary when no other disease coexists or secondary when another rheumatic disease is present (usually SLE). Finally, catastrophic APS is a rare form of APS with high mortality. In Fig. 7.18a, a patient with catastrophic APS developed thrombosis of the superior vena cava. Note the distended veins in the skin over the chest wall. She also has cicatrices where the tracheostoma was present while she was in the intensive care unit (ICU). Figure 7.18b shows a patient with secondary APS and thrombosis of the inferior vena cava. These patients have to be on a lifelong use of warfarin.



Fig. 7.19 Alopecia in systemic lupus erythematosus

Alopecia is an exaggerated form of hair loss, usually involving the scalp, but other body areas can be affected such as the eyebrows, eyelashes, beard etc. Alopecia may be diffuse or patchy, most of the cases reversible or permanently scarring as a result of discoid lesions in the scalp (Fig. 7.19a–f).

The patients in Fig. 7.19e, f have a permanent form of alopecia associated with the scarring DLE lesion. The rest of the patients have a transient hair loss due to exacerbation of their lupus disease process (of different extent). SLE patients may experience a diffuse, non-scarring, transient hair loss which can be acute or chronically associated with continuing lupus disease activity. When the flare of the disease subsides, normal hair growth resumes and in some cases the alopecia disappears.

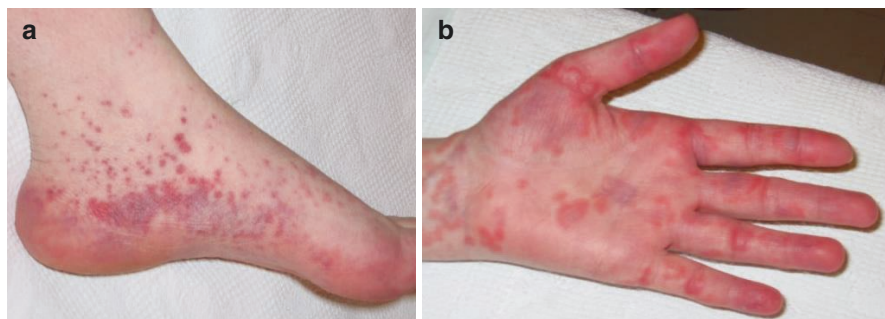


Fig. 7.20 Small vessel vasculitis in systemic lupus erythematosus

Small vessel vasculitis in SLE may present as palpable purpura, urticaria, petechiae as well as other forms of skin lesions. Vasculitis in SLE may affect skin but also internal organs (visceral vasculitis). Most common form of SLE vasculitis is cutaneous vasculitis whereas visceral vasculitis, which most of the times is more severe than cutaneous, has been described in less than 10% of cases. In addition, visceral vasculitis mostly coincides with systemic flares of the disease and may follow cutaneous vasculitis or may appear at the same time. In Fig. 7.20a and b, purpuric and urticarial-like rashes are presented respectively. Purpuric lesions result from damage to the vessel wall, sufficient to cause haemorrhage and oedema in the surrounding tissue. Urticarial vasculitis is an eruption of erythematous wheals that clinically resemble urticarial but histologically shows changes of leukocytoclastic vasculitis. These changes are characteristic of small vessel vasculitis.

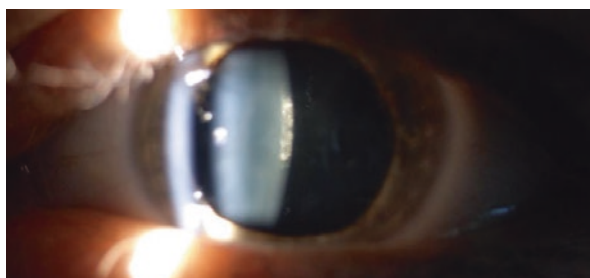


Fig. 7.21 Ocular manifestation in systemic lupus erythematosus

Cataract is the most common ocular damage in SLE. This figure shows a 30-years old female suffering from SLE with cataract due to different dosage schemes of CS for disease control.

Fig. 7.22 Shrinking lung syndrome

SLS is a rare complication of SLE. It is characterised by unexplained dyspnoea, a restrictive pattern on pulmonary function tests and elevated hemidiaphragms in the absence of any evidence of interstitial lung disease or hepatic enlargement. In some cases, SLS is associated with pleurisy, involving the diaphragmatic pleura or with myositis, affecting the muscles of the diaphragm. CS is the mainstay of treatment in these cases. This chest x-ray (CXR) shows elevation of both hemidiaphragms (right more than left) and bilaterally reduced lung volumes.

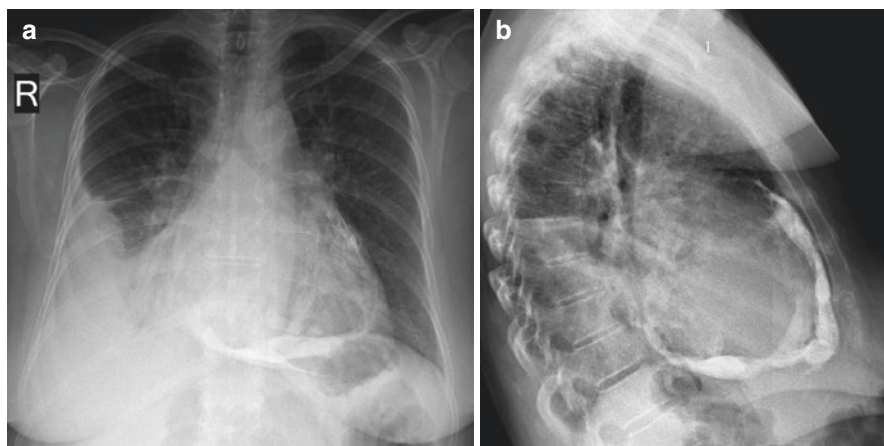


Fig. 7.23 Calcific constrictive pericarditis in systemic lupus erythematosus

This is a female patient with SLE and recurrent episodes of serositis (pleural and pericardial effusions). Calcific constrictive pericarditis is a rare finding consisting of pericardial calcifications. Usually, the presence of pericardial calcification on a plain radiograph strongly suggests constrictive pericarditis in patients with heart failure. However, the cause of constrictive pericardial disease is indeterminate and is often associated with idiopathic disease but systemic autoimmune diseases have been also implicated. Pericardial calcification is an independent predictor of increased peri-operative mortality rates.

Figure 7.23a, b show the calcified pericardium in a posteroanterior and lateral view respectively. On auscultation, the breathing sounds were decreased on the right lung base, while on percussion, a well-demarcated dullness (Damoiseau-Ellis line) was obtained. On the chest x-ray, a large pleural effusion of the right lung base was revealed.

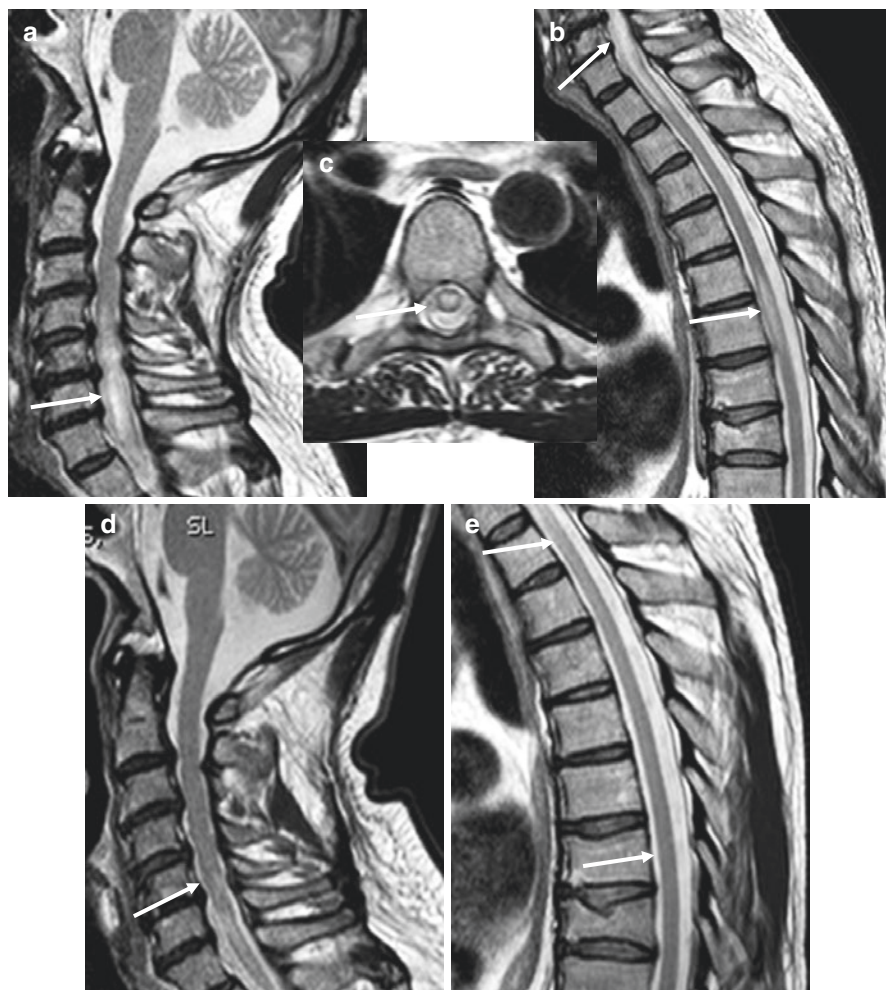


Fig. 7.24 Transverse myelitis and systemic lupus erythematosus

Transverse myelitis (TM) is a severe complication of SLE and is due to inflammation of the spinal cord. It develops suddenly and progresses rapidly in hours or days. Clinical manifestations include pain and muscle weakness, numbness and paralysis of the upper and lower extremities. Treatment with CS and CP may resolve disease progression. A magnetic resonance imaging (MRI) of a patient with SLE and TM is shown in Fig. 7.24. Sagittal T2-weighted images (a, b) and axial (c) reveal oedematous spinal cord with high signal (arrows) from the level of the fourth cervical body until the second thoracic body. A second MRI after a 6-month treatment with CS reveal almost complete remission of the spinal cord lesions (d, e).

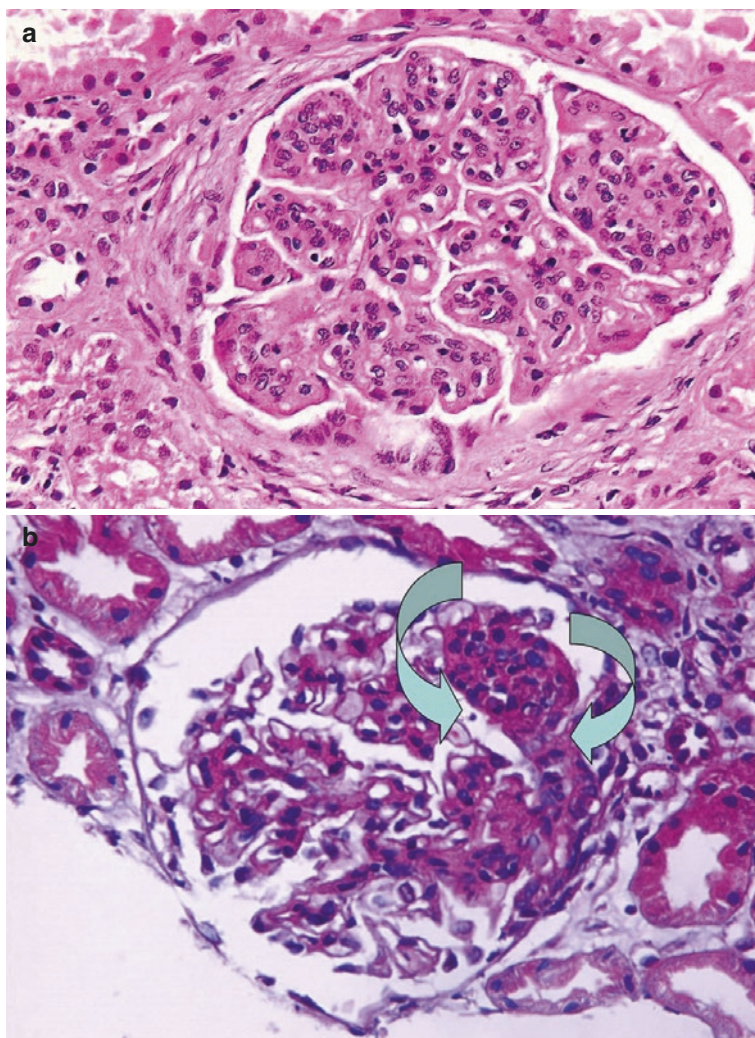


Fig. 7.25 Lupus nephritis – stage III/IV

Global segmental endocapillary proliferation. Glomerulus with lesions of global endocapillary proliferation.

Global is the term used to describe an endocapillary proliferation that affects $\geq 50\%$ of a glomerulus (Fig. 7.25a – HE $\times 400$).

Segmental (within the green arrows) endocapillary hyperplasia.

Segmental is the term used to describe an endocapillary proliferation that affects $<50\%$ of a glomerulus (Fig. 7.25b – HE $\times 400$).

Endocapillary proliferation is the characteristic glomerular lesion of lupus nephritis stage III (if the lesion is focal: $<50\%$ of the glomeruli) or stage IV (if the lesion is diffuse: $\geq 50\%$ of the glomeruli).

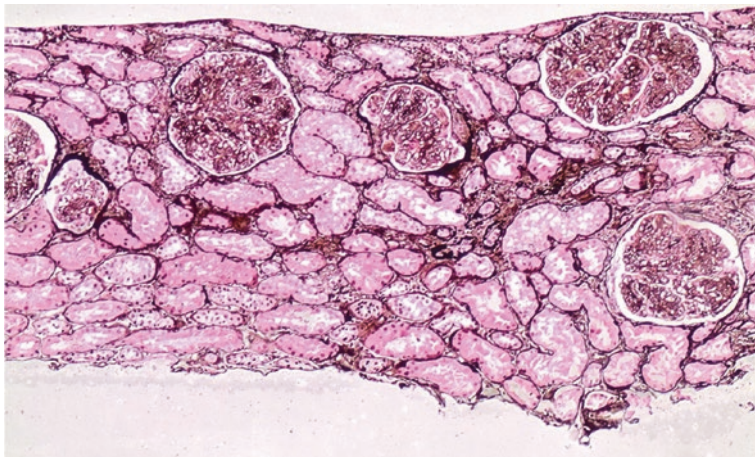


Fig. 7.26 Lupus nephritis – stage IV/V

Lupus nephritis stage IV-G: diffuse global endocapillary proliferation involving all the glomeruli in this biopsy (Jones methenamine silver $\times 100$).

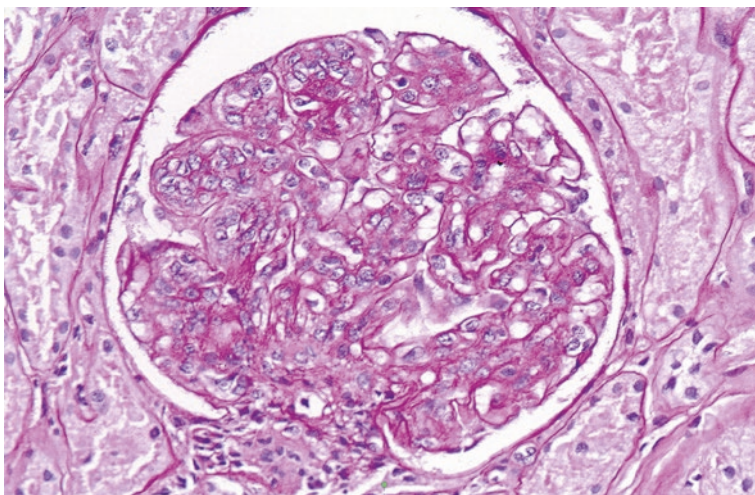


Fig. 7.27 Lupus nephritis – stage IV/V $\times 400$

Lupus nephritis stage IV-G: endocapillary hyperplasia with capillary basal membrane thickening (Pas $\times 400$).

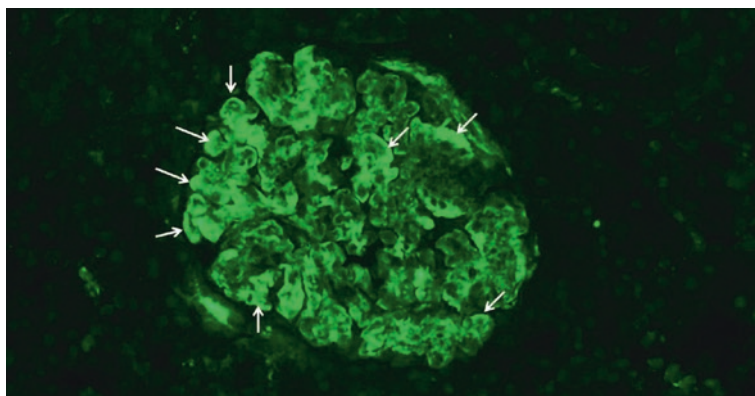


Fig. 7.28 Lupus nephritis – immunofluorescence

Global C1q large subendothelial deposits (mainly). Wire-loop deposits are shown which represent homogenous and rigid thickening of peripheral capillary loops due to subendothelial immune deposits (white arrows – $\times 200$). This is a stage IV, full-house pattern in immunofluorescence.

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Chapter 8

Scleroderma



8.1 Introduction

Scleroderma or systemic sclerosis (SCL) is an autoimmune disorder of unknown aetiology, characterised by fibrosis and microvascular injury in affected organs. The hallmark of the disease is thickening and tightness of the skin and of subcutaneous tissue. SCL may be confined to the skin (localised) or it may be generalised (systemic sclerosis). In the generalised form, involvement virtually of any organ systems can occur, most importantly the skin, blood vessels, lungs, kidneys, gastrointestinal tract, and the heart. SCL is further subdivided into limited and diffuse (depending on the extent of cutaneous involvement). A subset of patients with limited SCL have prominent calcinosis cutis, Raynaud's phenomenon (RP), esophageal dysmotility, sclerodactyly and telangiectasias and is called CREST syndrome. However, these features may also be seen in patients with diffuse SCL.

Hippocrates was the first to describe the illness as "thickened skin". The first detailed description of the disease was by an Italian doctor named Carlo Curzio in the mid 1700s, but the term "scleroderma" was first coined by Giovambattista Fantonetti in 1836.

8.2 Epidemiology

The prevalence of SCL in the general population varies among different regions. In Britain the reported prevalence is 35 cases per million adults whereas in the United States approximately 240 cases per million adults. There is a female to male preponderance with different studies reporting from 3:1 to 8:1 (7:1 in early adult life).

8.3 Aetiopathogenesis

There is no clear obvious cause for SCL. Genetic predisposition appears to be limited. SCL is rather common in coal and gold miners, and in workers exposed to vinyl-chloride, epoxy resins and aromatic hydrocarbons. Furthermore, individuals taking pentazocin, bleomycin and products containing L-tryptophan develop SCL-like features. The pathogenesis involves a complex interplay between endothelial cells, fibroblasts and the immune system triggered by an environmental factor. It seems that vascular injury causes endothelial cell activation and platelet aggregation and activation. These promote the recruitment of activated lymphocytes, production of Th-2 cytokines like transforming growth factor beta (TGF- β), fibroblast activation, leading to collagen production, accumulation and tissue fibrosis.

8.4 Classification Criteria

In 2013, the American College of Rheumatology (ACR) in collaboration with the European League against Rheumatism (EULAR) developed classification criteria for SCL and superseded the 1980 ACR criteria due to poor sensitivity. The 2013 ACR/EULAR reported sensitivity is 91% and the specificity 92%. These criteria are applicable to any patient considered for inclusion in a SCL study and thus are not diagnostic criteria. Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal (MCP) joints (9 points), puffy fingers (2 points), sclerodactyly of the fingers (4 points), digital tip ulcers (2 points), fingertip pitting scars (3 points), telangiectasia (2 points), abnormal nail-fold capillaries (2 points), pulmonary arterial hypertension (PAH)(2 points), interstitial lung disease (ILD)(2 points), RP (3 points), anticentromere antibodies (ACA), anti-topoisomerase I (anti-Scl-70) antibodies, and anti-RNA polymerase III antibodies (maximum score is 3 if more than one positive antibodies), all are part of the classification criteria. If a sum of 9 and above points are collected, then it is classified as SCL.

8.5 Signs and Symptoms

Signs and symptoms differ depending on the extent of skin sclerosis, severity of the vasculopathy and type of organ involvement.

Skin manifestations: skin involvement is the hallmark feature of SCL patients. It is characterised of skin thickening and hardening. Fingers, hands, and face are generally the earliest areas affected. Cutaneous changes usually begin with an early phase of skin oedema, manifested as swollen fingers and hands. Patients which develop rapidly sclerotic changes are at greater risk of serious organ involvement such as pulmonary fibrosis and renal failure. Skin thickening and atrophy appears typically after 3–5 years, and flexion contractures develop over joints. Telangiectasias are also another feature of SCL. They typically appear on hands, face and anterior upper chest. Microstomia and microcheilia can give a fish-mouth appearance and can interfere with eating, speaking and oral hygiene activities. Calcinosis cutis consists of abnormal calcium deposition in soft tissues and it can be present in about one third of patients with SCL.

Vascular manifestations: vascular dysfunction is a significant component of the pathogenesis of SCL. The most characteristic clinical manifestation of vascular dysfunction is RP. RP is an episodic, reversible, sequential expression of pallor, cyanosis, and redness of the digits occurring as an attack in response to cold exposure, temperature variation or stressful stimuli. RP may be the earliest manifestation of the disease and may precede the disease onset for months to even years. Nailfold videocapillaroscopy (NVC) is a useful tool used in the evaluation of

microcirculation. Capillaroscopic abnormalities typical of the disease include enlarged capillaries and capillary loss with or without capillary haemorrhages. Digital ulcers, are necrotic lesions that occur in up to 50% of patients with SCL and typically appear on the fingertips.

Musculoskeletal manifestations: arthralgia and arthritis are observed in more than half of cases. MCP and proximal interphalangeal (PIP) arthritis are relatively frequent. Carpal tunnel syndrome (CTS) and tendon friction rubs are the consequence of the fibrosis of the tendons. When severe damage and fibrosis occur at the same time, an acro-osteolysis with resorption of the distal phalanx can be observed, due to microvascular injury and tissue ischaemia.

Pulmonary manifestations: interstitial lung disease followed by pulmonary interstitial fibrosis is more frequently seen in patients with diffuse SCL. Exertional dyspnoea is the most common symptom referred by the patients at an early stage of the disease. Later on, dyspnoea with exertion and diminished exercise tolerance, fatigue, chest pain, and occasionally syncope may be warning signs of pulmonary arterial hypertension which has a very poor prognosis. Patients with limited SCL are at high risk of developing isolated pulmonary arterial hypertension (without interstitial lung disease).

Gastrointestinal manifestations: gastrointestinal involvement is highly common in SCL patients. Gastroesophageal reflux, dysphagia and heartburn in the epigastric and retrosternal region are common. Esophageal disease results in reflux esophagitis, esophageal peptic strictures, and even Barrett's oesophagus.

Renal manifestations: SCL renal crisis is seen in about 5% of patients with SCL and is characterised by abrupt onset of oliguric renal failure, abrupt onset of hypertension, bland urinary sediment.

Cardiac manifestations: pericardial effusions, myocardial fibrosis with diastolic dysfunction as well as premature coronary artery disease may occur.

8.6 Differential Diagnosis

The presence of thickened skin, distinguishes scleroderma from other connective tissue diseases. SCL-like skin induration can occur in various disorders and is an imperative to differentiate these conditions from scleroderma. These conditions include scleroedema and diabetic scleroedema, scleromyxoedema, nephrogenic fibrosing syndrome, diffuse fasciitis with eosinophilia, chemically induced scleroderma-like conditions, chronic graft-versus host disease and paraneoplastic syndromes. Thus, an accurate past medical history, detailed clinical examination and the appropriate laboratory and imaging tests are useful to differentiate the above conditions from scleroderma patients.

8.7 Diagnostic Modalities

Imaging: plain radiography and High-resolution Computed Tomography (HRCT) are the most used imaging techniques used to diagnose and monitor early lung involvement. Chest radiographs are insensitive to early changes, but changes of pulmonary fibrosis become evident at a later time. On HRCT, SCL may appear in either a usual interstitial pneumonitis (UIP) or non-specific interstitial pneumonitis (NSIP) pattern. Plain radiographs are also used to evaluate for presence of soft-tissue calcifications.

Pulmonary function tests: decrease in diffusing capacity and restrictive abnormalities are common findings especially in severe SCL.

Nailfold videocapillaroscopy (NVC): it is a useful tool for patients with RP. There are three different scleroderma patterns of microvascular damage, including the “early”, “active”, and “late” pattern. Enlarged/giant capillaries, capillary haemorrhages, capillary distribution, ramified capillaries and absent capillaries are some characteristic findings seen in SCL.

Laboratory: *Anti-nuclear antibodies* (ANA) are positive in the majority of cases. *Anti-topoisomerase-1 (Scl-70)* is seen in diffuse SCL associated with interstitial pulmonary fibrosis. *ACA* are seen in the limited SCL. *Anti-polymerase-III* are seen in patients with diffuse SCL with cardiac or renal disease.

Thrombocytopenia, proteinuria and an elevated creatinine may be seen in SCL renal crisis.

8.8 Management

Treatment of SCL is a difficult task. The first step is to treat the vascular component of the disease, starting from the RP and/or pulmonary hypertension. The cornerstone of therapy is to maintain the body and the extremities warm and to advise patients to avoid physical and psychological stress. Calcium-channel blockers are the initial medical treatment, followed by endothelin inhibitors like bosentan, or 5-phosphodiesterase inhibitors like sildenafil or/and prostanoid analogues. The second step is to treat systemic disease manifestations and internal organ involvement. To this end, corticosteroids (CS), methotrexate (MTX), mycophenolate mofetil (MMF) and cyclophosphamide (CP) are used.

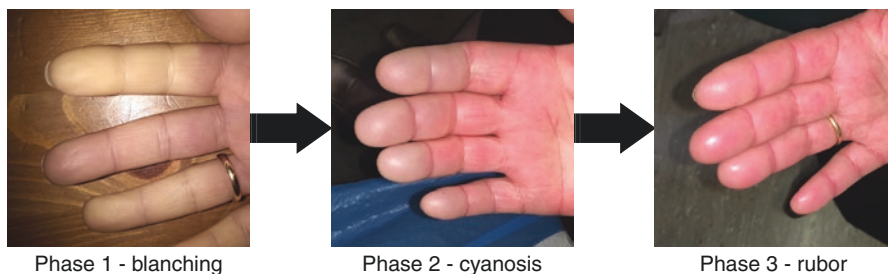


Fig. 8.1 Secondary Raynaud's phenomenon

RP develops in >90% of patients with systemic sclerosis, often predating the onset of other symptoms and signs. NVC is a validated tool that can differentiate primary from secondary RP (see Fig. 8.3 with images from NVC).

Usually there are three distinct phases in RP (but occasionally only two phases may appear):

Phase 1: blanching (vasospasm of artery results in vascular occlusion).

Phase 2: cyanosis (capillaries and venules dilate in response to ischaemia and are filled with deoxygenated blood).

Phase 3: rubor/redness (relaxation of vasospasm: capillaries are still dilated, but are now carrying oxygenated blood).

Chilblains (bottom figure) is a condition that sometimes can be confused with RP, thus, it is important to differentiate between the two conditions. Chilblains are caused by an abnormal skin reaction to cold. They tend to occur on toes, fingers, nose and earlobes but other skin areas may be affected. These lesions typically present as painful erythrocyanotic skin discolorations which disappear on rewarming of the affected skin area. In some instances, it may be difficult to differentiate chilblains from RP, especially when the latter appears as a two-phase phenomenon.





Fig. 8.2 Raynaud's phenomenon – clinical images

Patients with different phases of RP. Figure 8.2a–d show patients with blanching of their fingers whereas Fig. 8.2e shows a patient on the cyanotic phase. Different stimuli may contribute to the appearance of RP such as exposure to cold, emotional stress or tobacco use.



Fig. 8.3 Nailfold capillary changes in scleroderma

Early SCL may produce diffuse swelling and stiffness of the fingers, which can resemble early rheumatoid arthritis (RA) hands. These findings (black arrows – Fig. 8.3a, b), are helpful in distinguishing SCL from RA. The cuticle is often ragged with enlarged capillary loops and visible microhaemorrhages.

NVC can reveal specific alterations of the capillary architecture.

Figure 8.3c *normal pattern* (regular arrangement of the capillary loops in the whole nailfold with normal capillary shape, number and diameter).

Figure 8.3d *active pattern* (frequent megacapillaries, capillary haemorrhages, moderate capillary loss and mild disorganisation).

Figure 8.3e *Late pattern* (capillary loss, absent megacapillaries or haemorrhages, disorganisation of the capillary architecture, capillary ramifications).



Fig. 8.4 Scleroderma facies – early manifestations

SCL patients on early disease stages. The so-called “scleroderma facies” becomes characteristic on more advanced stages (*see below*), with a generalised “pinched” look, microstomia and fissures radiating from the mouth. Figure 8.4a–d depict patients with SCL facies in early stages with a few telangiectasias on the face (black arrowheads) as well as circumoral puckering (black arrows). In some instances, the circumoral puckering, especially in the elderly where there are skin wrinkles, may not be easily distinguished as in Fig. 8.4d.



Fig. 8.5 Scleroderma facies – advanced stages

SCL patients on advanced disease stages. Here the SCL facies' characteristics are more evident. As disease progresses, telangiectatic lesions may be more pronounced (Fig. 8.5a–e). Also, circumoral puckering is more evident with fissures radiating from the mouth. Figure 8.5f shows a patient with prominent telangiectasias on the face and a steroid facies.

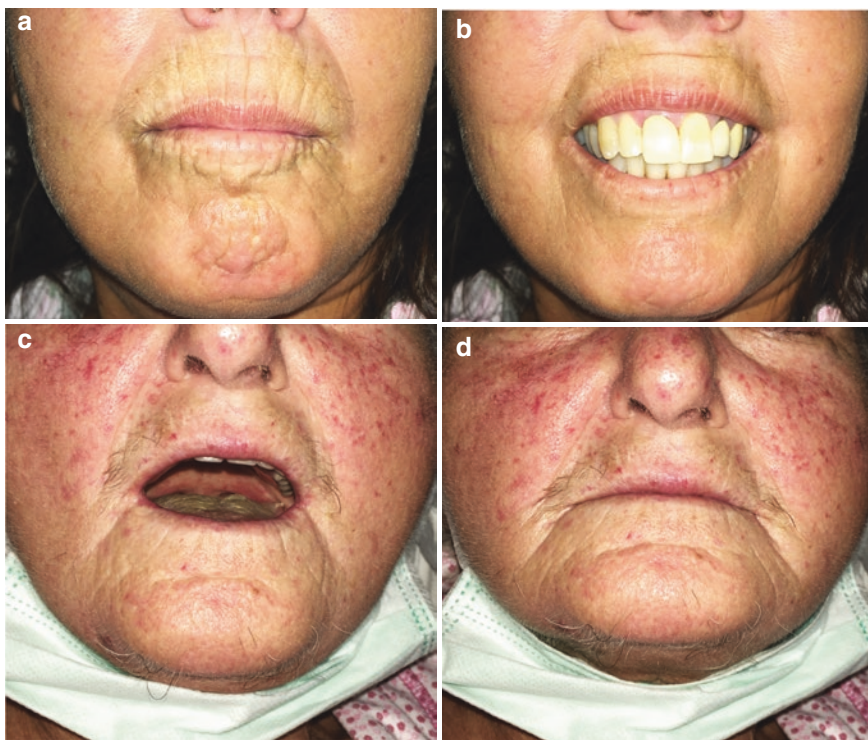


Fig. 8.6 Microstomia

In some advanced cases the patients are unable to fully open their mouth due to sclerosis of the circumoral tissues leading to microstomia or the so-called “fish-mouth”. In these figures, two different patients with microstomia are shown (Fig. 8.6a–d). Difficulty in eating and bad oral hygiene may develop. Note the circumoral puckering and the telangiectatic lesions of the skin.

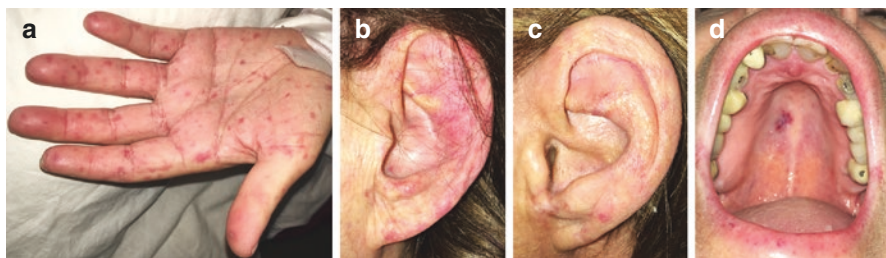


Fig. 8.7 Telangiectasias

Telangiectasias are common manifestations of microvascular changes in SCL (limited and diffuse subtypes). They can develop on any skin surface but they appear primarily on the fingers, hands, face, and mucous membranes. They may also appear on the limbs and trunk. In Fig. 8.5, telangiectatic changes in different stages can easily be seen on the face of the patients. Figure 8.7a shows numerous telangiectasias on the palmar surface of the left hand of a patient with limited SCL. Figure 8.7b, c show two different patients with telangiectasias on the ears. Finally, in Fig. 8.7d, telangiectatic findings appear on the lips and the hard palate.



Fig. 8.8 Atrophie blanche (Milian's white atrophy)

Atrophie blanche is a smooth ivory white plaque, slightly depressed surrounded by a pigmented telangiectatic area. It is usually localised in the lower limbs and mostly affects middle-aged women. Atrophie blanche is not an exclusive finding to SCL patients. It can be present in other rheumatic conditions such as systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), polyarteritis nodosa (PAN) and RA but more frequently in chronic venous insufficiency, with or without ulceration. In Fig. 8.8a and b, two different patients with the characteristic manifestation are shown.

Fig. 8.10 Prayer's sign

Figure 8.10a, b show two patients with swelling and sclerosis of both hands due to SCL. These patients are unable to place the palmar surfaces together (prayer's sign – black arrow). This sign is not pathognomonic for scleroderma as it can be seen in diabetic cheiroarthropathy/sclerodactyly (more commonly in type 1 diabetes) as well as in SCL (when hands are affected).

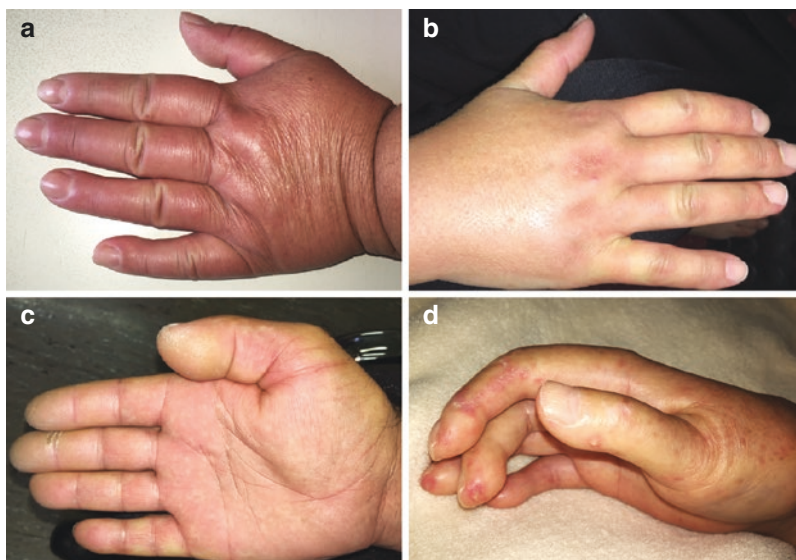


Fig. 8.9 Skin phases of scleroderma

On early SCL, there is swelling of fingers and toes (non-pitting oedema), which is a common early sign (puffy hands – oedematous phase). Digits have a sausage-like appearance (Fig. 8.9a). There may be marked stiffness, sometimes resembling RA. Then, skin, especially of the fingers, becomes hard and thickened (sclerodactyly) and there is a limited joint movement. There is a slow progression to waxy thickening (indurative phase – Fig. 8.9b, c) and tethering of the skin over the fingers. The last phase is the atrophic phase where skin becomes thin and atrophic after many years (Fig. 8.9d). RP is present in >90% of patients and the hands present intense vasomotor changes, even in small pressure. A simple attempt to force them flat onto a surface, typical blanching around the knuckles develops.

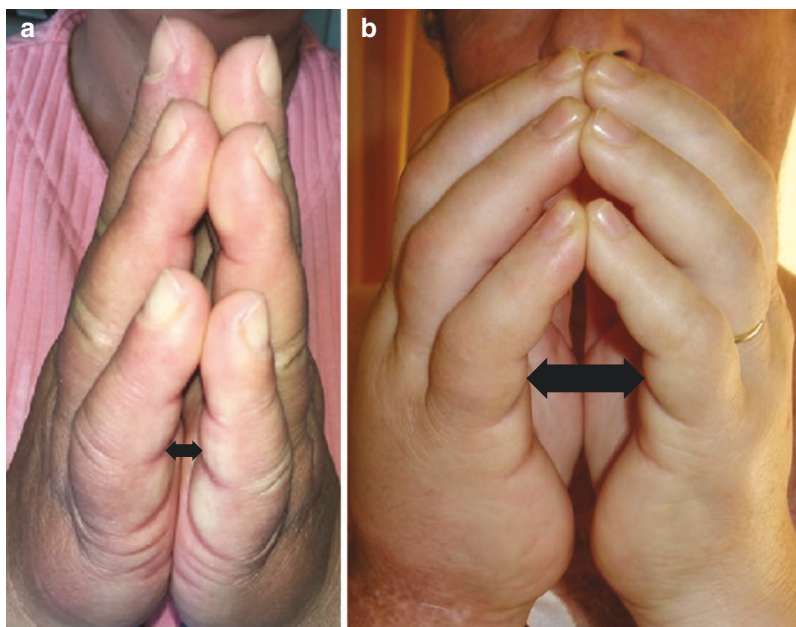




Fig. 8.11 Vascular manifestations in scleroderma

Vascular manifestations are a significant component of SCL. It starts with RP. Repeated attacks of RP cause ischaemia and as a consequence of these skin vasculitic lesions ulcers and gangrene of the affected limbs may develop. Vascular manifestations affect the skin, lungs, kidneys and other organs. In Fig. 8.11a–c different types of skin lesions affecting the digits of hands and feet are shown. You may also note the digital ulcer development and severe fixed flexion deformities shown in Fig. 8.11d–f. The hand and foot involvement may progress to produce severe fixed flexion deformities (mostly) of the fingers (black arrowheads – see also Fig. 8.12). Moreover, repeated and severe attacks of RP lead to ulceration of the finger tips or tips of the toes (yellow arrows) and loss of the finger pads (Fig. 8.11e, f – yellow arrowheads).



Fig. 8.12 Advanced cases of scleroderma

Not all SCL patients present the same progression of the disease or the same clinical findings. Patient in Fig. 8.12a–c, has severe restriction of finger movements and partial loss of the finger pads (atrophic phase, note the waxy appearance in Fig. 8.12c of the index finger). In Fig. 8.12d, this patient had a total loss of finger mobility due to severe skin thickness. There are numerous telangiectatic lesions but no ulcerations. In Fig. 8.12e, the ulcerations are more prominent on feet. Patient in Fig. 8.12f and g, has severe loss of the finger pads and numerous palmar telangiectatic lesions.

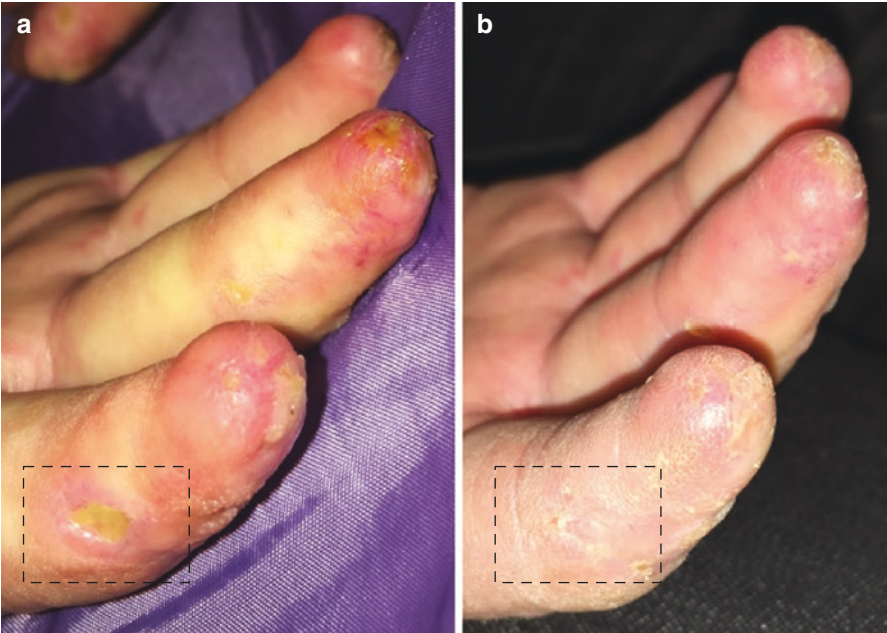


Fig. 8.13 Treatment of ischaemic digital ulcers in systemic sclerosis (**a** – before treatment, **b** – after treatment)

This 63-year old patient was treated with intravenous infusions of a prostacyclin-stable analogue due to severe ischaemic digital ulcers. There was significant improvement on a follow-up (40 days after the last infusion). The ulceration of the lateral side of the index finger appears to have a complete healing (black rectangle), the colour of the fingers has been improved as well as the circulation at the tips of the fingers.

Fig. 8.14 Clinical assessment of skin thickening

The Modified Rodnan Skin Score (mRSS) is usually used for studies to follow SCL patients. The mRSS uses a 0–3 scale (0: normal skin, 1: mild thickness, 2: moderate thickness, 3: severe thickness with inability to pinch the skin into a fold) and divides the skin in 17 surface areas (fingers, hands, forearms, arms, feet, legs, thighs, face, chest and abdomen). These individual values are added and the sum is defined as the total skin score.

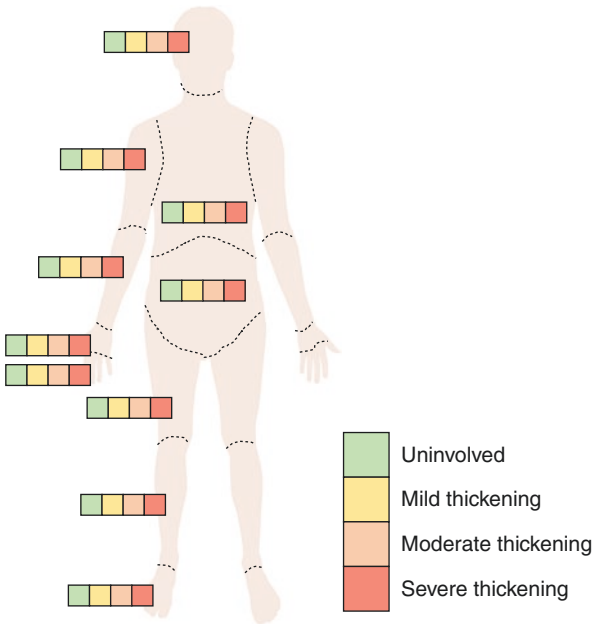


Fig. 8.15 Non-digital lower extremity ulcers
This patient was suffering from diffuse SCL. Non-digital lower extremity ulcers are a difficult to treat complication of SCL, and a significant cause of morbidity. They reflect a chronic underlying vasculopathy associated with delayed wound healing in SCL patients. Unfortunately, this limb was amputated because of refractory to healing extended ulcers and recurrent episodes of wound infection.



Fig. 8.16 Gangrene and amputation

SCL patients with poor circulation and no response to current treatment schemes, often develop gangrene and amputation of the affected limb is mandatory. The patient in Fig. 8.16a despite treatment with intravenous prostacyclin analogues, 5-phosphodiesterase inhibitors, endothelin inhibitors and nifedipine, failed to respond to treatment and the result is the amputation of the finger as shown in Fig. 8.16b. Note also other severe necrotic skin changes affecting other parts of the body in different patients (Fig. 8.16c–e).

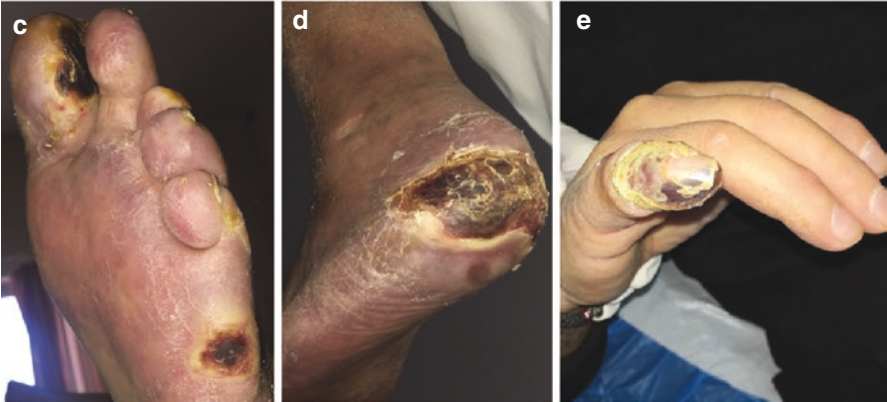


Fig. 8.16 (continued)





Fig. 8.18 Calcinosis in systemic sclerosis

Calcinosis cutis in SCL most commonly occurs on the hands (Fig. 8.18a, b), or near joints such as elbows or knee (Fig. 8.18c, d), although they may appear anywhere (Fig. 8.18e–g). Calcinosis may range from one very tiny deposit, to large clusters, which are usually painful. Gross deformities, with mild loss of the terminal phalanges and widespread large calcinotic deposits can be seen in these x-rays. The patient is disabled by severe limitation of movements of the main joints and pain.



Fig. 8.17 Necrotic skin lesions due to severe Raynaud's phenomenon

Ischaemic lesions especially of the fingers and toes used to be more prevalent in the past. Nowadays, there are more treatment options regarding the microcirculation. In Fig. 8.17a and b, a digital ischaemia of the 4th toe that led to gangrene in a patient working in low temperatures is shown. Note also the colour of the 3rd toe in Fig. 8.17b which appears cyanotic. In Fig. 8.17c, another patient with SCL and necrotic lesions of the fingers after skiing in low temperature.

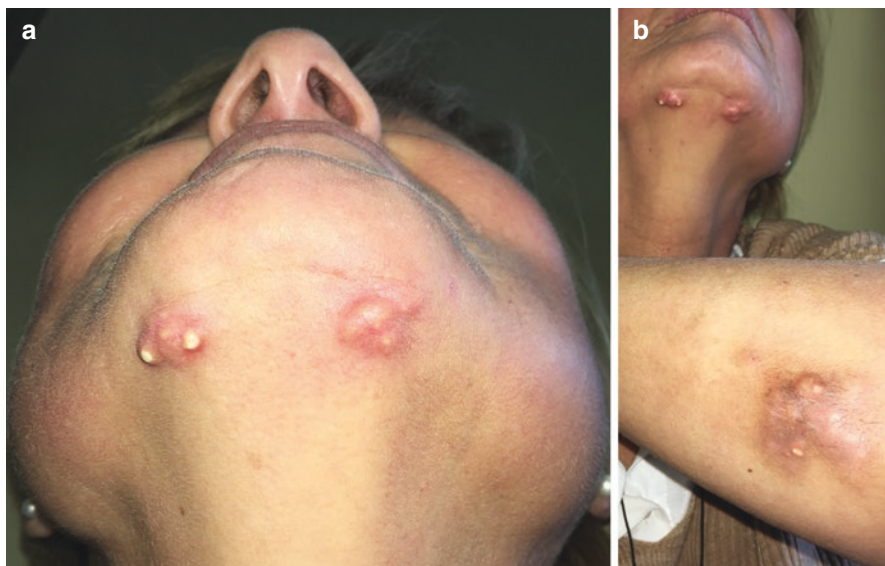


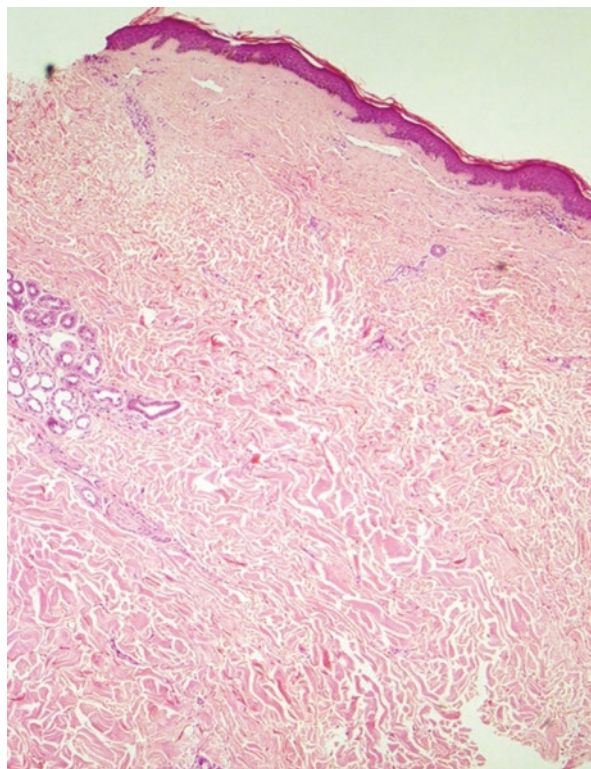
Fig. 8.19 Calcinosis in systemic sclerosis

As described in Fig. 8.18, calcinosis cutis in SCL patients may affect any part of the body. The lesions in Fig. 8.19a appear as firm, whitish/yellowish multiple nodules on the surface of the skin. A discharging chalk-like creamy material consisting mainly of calcium phosphate appears when the skin ulcerates. The same patient had multiple lesions on different parts of her body (Fig. 8.19b).

Fig. 8.20 Scleroderma

histology – skin biopsy

The collagen bundles are thickened, the number of fibrocytes is decreased. A scant lymphocytic infiltrate and mucin throughout the reticular dermis are observed (H/E, $\times 40$).



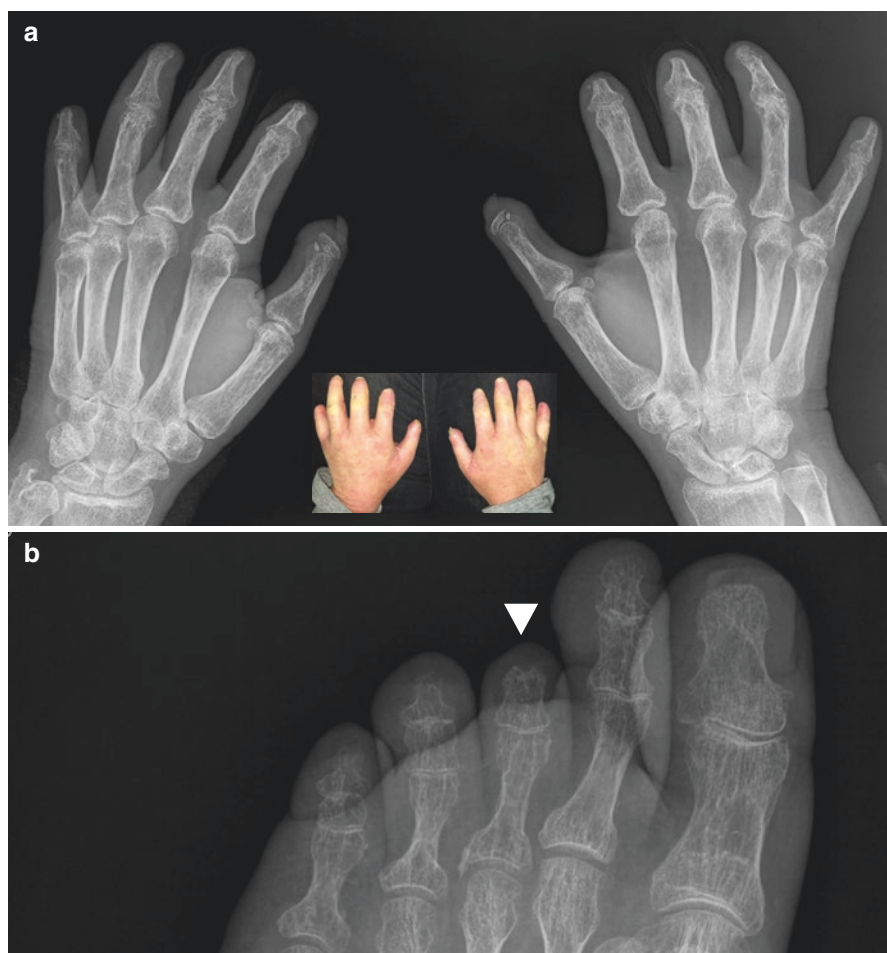


Fig. 8.21 Acro-osteolysis

Acro-osteolysis is the resorption of the distal phalanges in patients with SCL. There is also periarticular osteoporosis. Interestingly, the patient in Fig. 8.21a presented with no distal phalanges and acro-osteolysis of the middle phalanges (digits 2–5). Compare the radiographic image with the clinical image in Fig. 8.12g (see also the insert picture). In Fig. 8.21b, acro-osteolysis of the distal phalanx of the middle toe is evident (white arrowhead).

Bone resorption may occur anywhere in systemic SCL, but it most commonly occurs in the fingertips and mandible. When acro-osteolysis affects the mandible, it can cause teeth to loosen and may also be associated with microstomia.

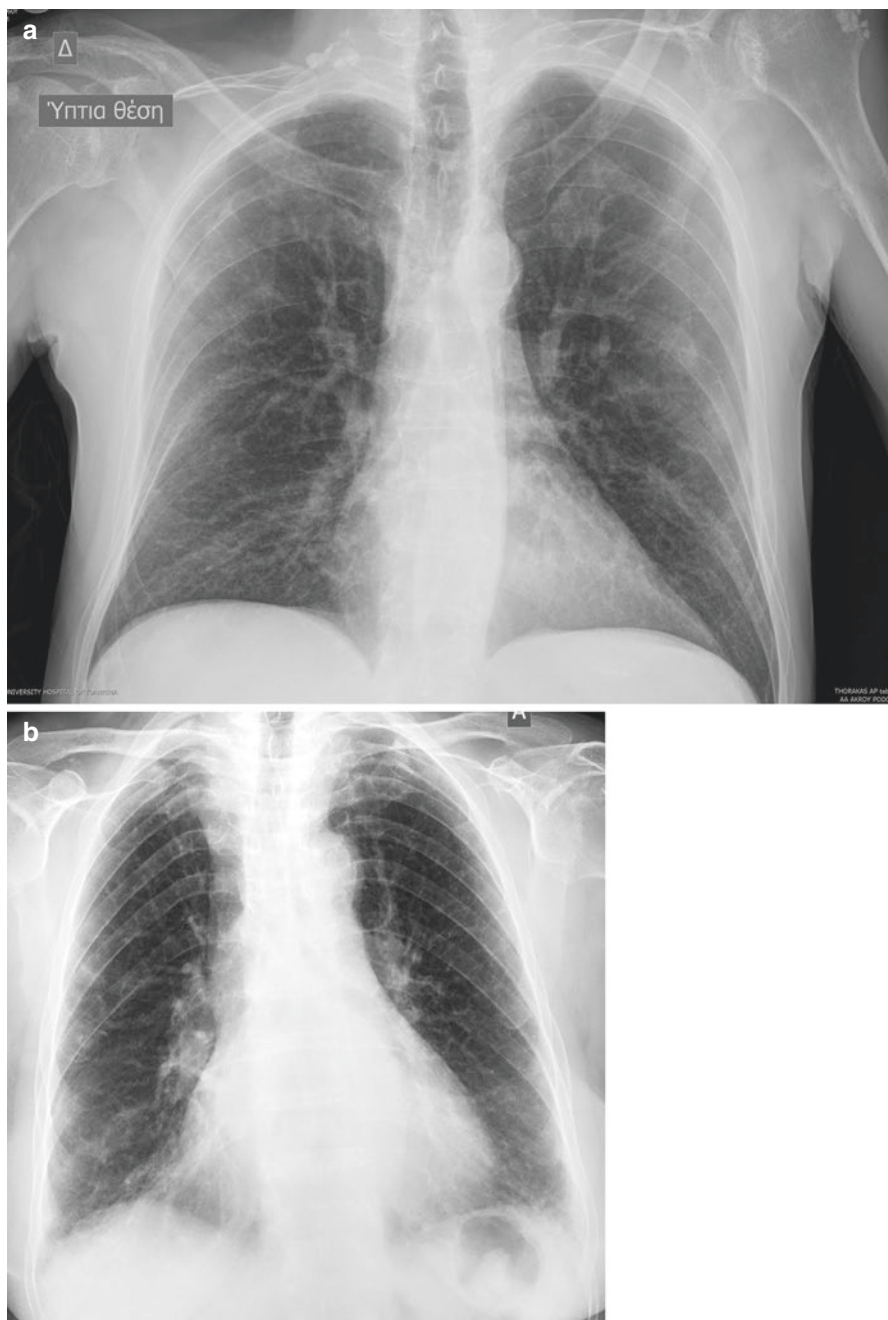


Fig. 8.22 Interstitial lung disease x-ray

Chest x-ray of a patient with SCL and interstitial lung disease. Note the bilateral reticular shadowing in Fig. 8.22a. A reticulo-nodular pattern is shown in Fig. 8.22b. There are also calcifications around the left humeral head (Fig. 8.22a). Chest x-rays are not sensitive to early changes and may appear normal despite respiratory function test abnormalities. HRCT is the imaging modality of choice.

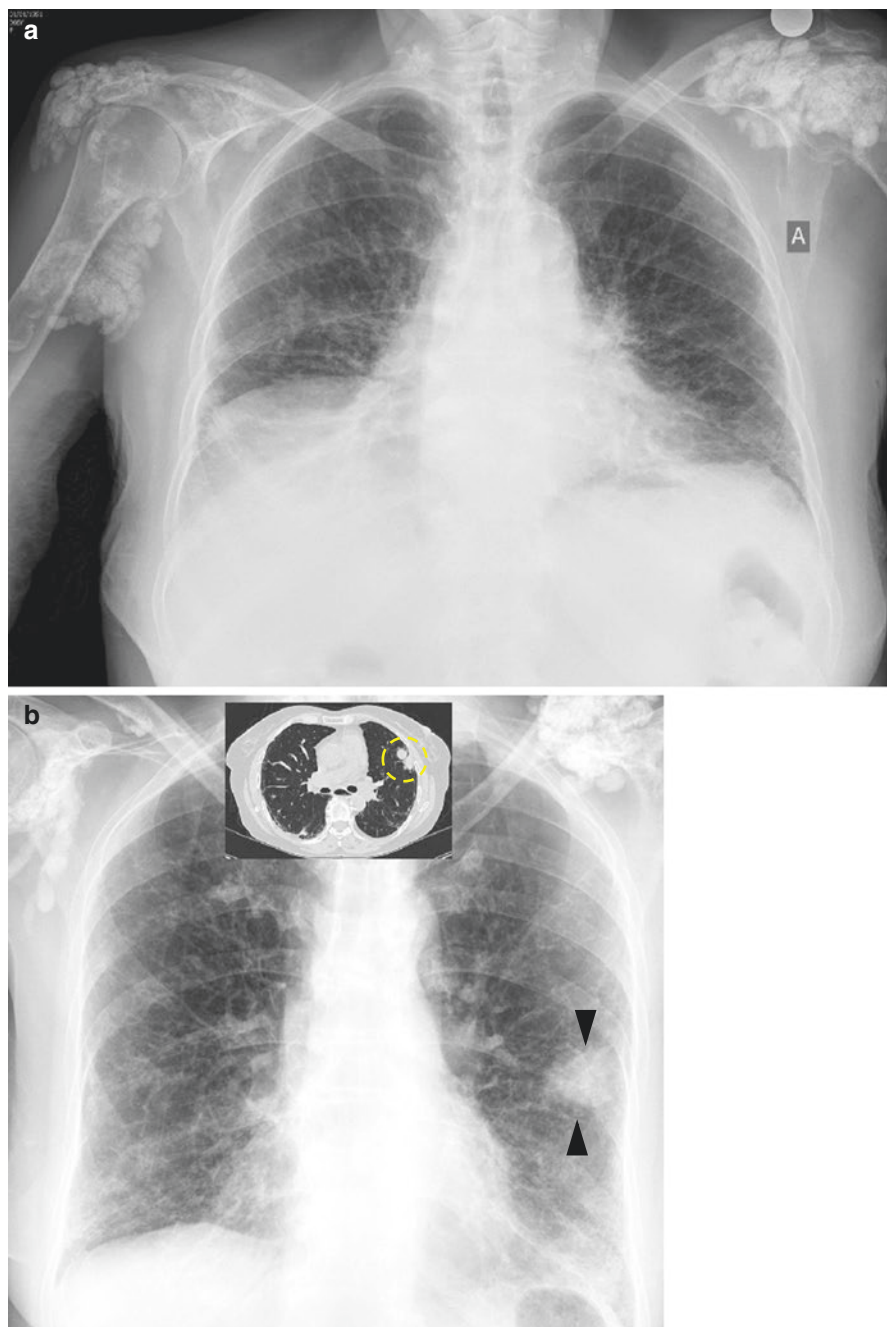


Fig. 8.23 Severe cases of lung involvement

In these two cases (Fig. 8.23a, b) changes of pulmonary fibrosis are evident. Extensive calcifications are also shown in the periarticular regions of the shoulders. In Fig. 8.23b, note also the opacity of the left lung (black arrowheads) which turned out to be lung carcinoma (see the CT of the same patient in the insert figure – yellow circle). There is an increased risk of carcinoma of the lung in patients with SCL, even among non-smokers.

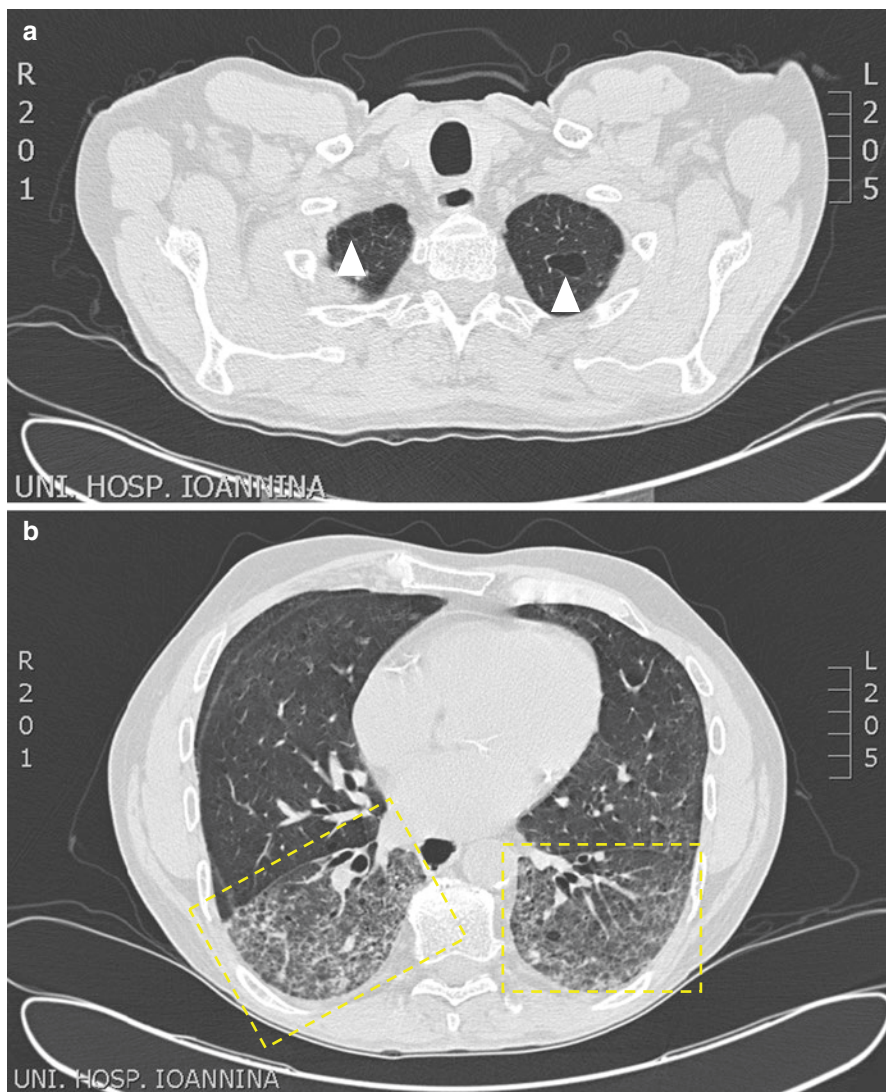


Fig. 8.24 Lung involvement – Combined pulmonary fibrosis and emphysema

HRCT from a male smoker SCL patient aged 59 years with combined pulmonary fibrosis and emphysema demonstrating upper-lobe emphysema (white arrowheads – Fig. 8.24a) and lower-lobe pulmonary fibrosis. Note the ground glass opacities (yellow dashed rectangles – Fig. 8.24b). The coexistence of emphysema and pulmonary fibrosis in the same patient is an increasing recognised clinical syndrome known as combined pulmonary fibrosis and emphysema (CPFE). CPFE is characterised by dyspnoea, upper-lobe emphysema, lower-lobe fibrosis, and abnormalities of gas exchange.

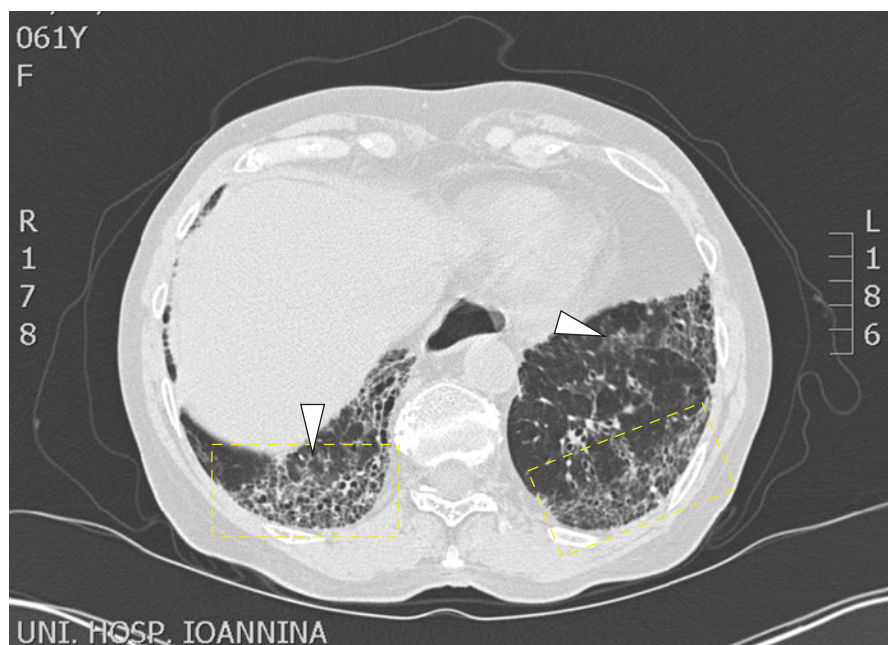


Fig. 8.25 Lung involvement – High resolution computed tomography
Pulmonary fibrosis in a 61-years female suffering from SCL. Honeycombing is evident in both lung bases (yellow dashed rectangles). Ground glass opacities (white arrowheads) and traction bronchiectasis can also be seen with intralobular interstitial thickening.

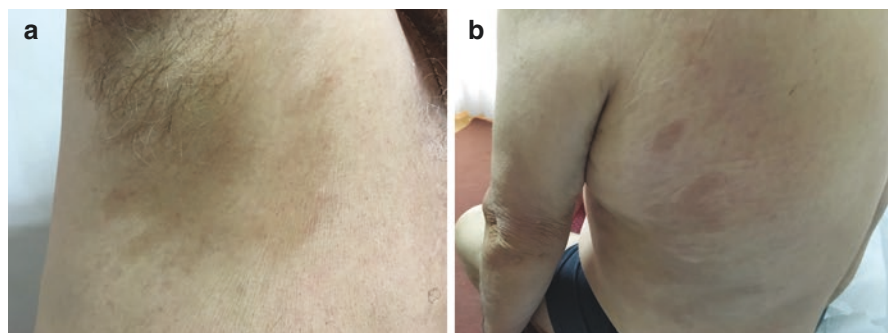


Fig. 8.26 Other types of scleroderma

Morphea and linear SCL (when the linear type affects the forehead then the term used is “en coup de sabre”) are classified under the term localised SCL. Morphea is a disorder characterised by thickening and induration of the skin and subcutaneous tissue due to excessive collagen deposition.

There are several different types of morphea (bullous, deep, generalised, guttate, keloid, profunda), but they tend to appear with no visceral involvement. The diagnosis is usually clinical and can be confirmed with a skin biopsy.

Figure 8.26a–c show patients with the plaque-type morphea (8.26a – right axillae, 8.26b – left shoulder, 8.26c, d – lateral side of the abdomen), whereas Fig. 8.26e shows a patient with the generalised form. The most common form is the plaque-type morphea.



Fig. 8.26 (continued)

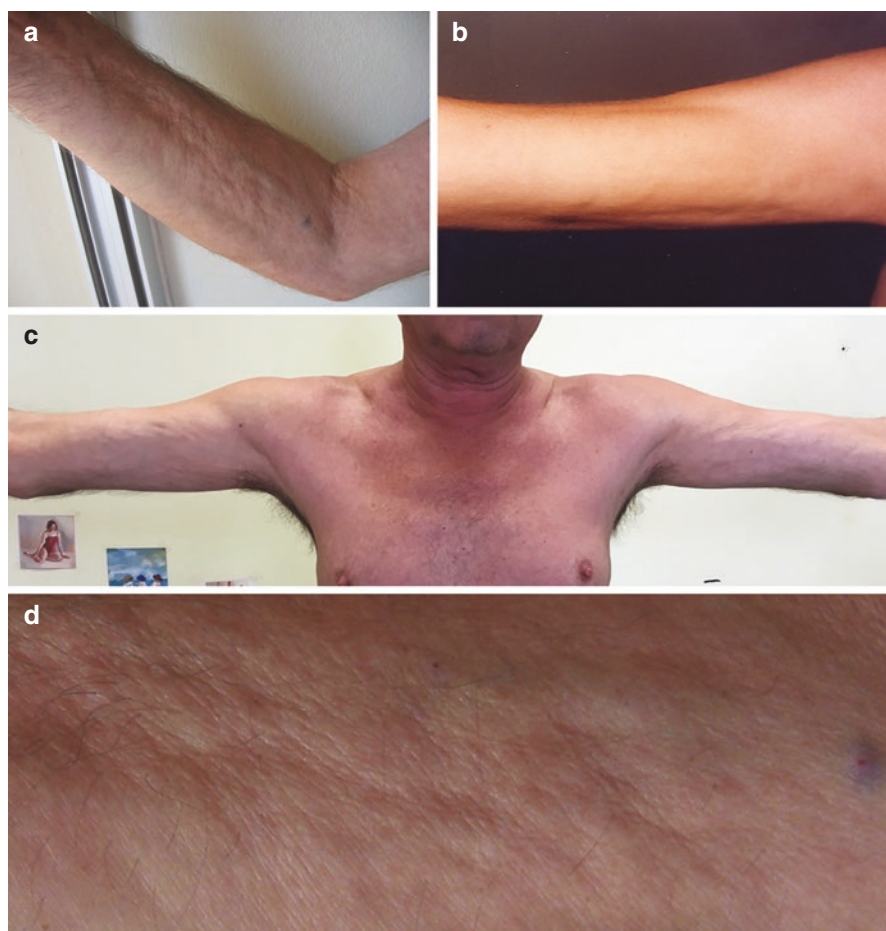


Fig. 8.27 Scleroderma-like disorders

The most clinically relevant scleroderma-like disorders include nephrogenic systemic fibrosis (NSF), scleroedema, scleromyxoedema and eosinophilic fasciitis (EF).

EF, also known as Shulman's disease is characterised by rapid onset of skin and muscle fascia thickening affecting mainly the arms, forearms and thighs sparing the hands and fingers. The skin has a "peau d'orange"-like appearance with the early development of flexion contractures particularly at the elbow, as seen in our patient in Fig. 8.27a. In Fig. 8.27b, a case with milder characteristics is presented, whereas in Fig. 8.27c, a patient with involvement of both arms is shown. Figure 8.27d shows the case from Fig. 8.27a in more detail. A deep biopsy that extends to the underlying fascia shows eosinophilic infiltrates affecting the fascia which is thickened. Peripheral eosinophilia is also common. Peripheral eosinophilia if present and a deep biopsy demonstrating eosinophilic infiltration will differentiate EF from SCL.

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Chapter 9

Inflammatory Myopathies



9.1 Introduction

The inflammatory myopathies (IM) are a group of heterogeneous disorders and include dermatomyositis (DM), polymyositis (PM), necrotising autoimmune myositis (NAM), and inclusion-body myositis (IBM). The main characteristic of these clinical entities is muscle weakness. DM and PM are characterised by the subacute onset of symmetric proximal muscle weakness and involvement of other organ systems such as lungs and skin, have a good response to immunosuppression and a strong association with autoantibodies. On the other hand, patients suffering from IBM, have symptoms from proximal but also distal muscles and typically the weakness is slowly progressive. IBM is not responding to immunosuppression as good as DM and PM. Other subtypes are dermatomyositis sine myositis (DSM) and overlap myositis (OM), a subtype which is beginning to be recognised in the literature. IM can occur as isolated inflammatory muscle disorders or associated with autoimmune rheumatic diseases like scleroderma (SCL), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) or neoplasias.

E. Wagner has described the first case of myositis in 1863, in a patient with muscle and cutaneous disorders. In 1875, P. Potain reported a similar case. It was H. Unvericht, in 1891, who coined the term DM, after reporting a peculiar muscle disease on a 27-year-old stonemason with fatigue and malaise, muscle pain and weakness, swelling on face, and bluish lesions over eyelids.

9.2 Aetiopathogenesis

As in many autoimmune diseases, the cause of IM is unknown, but the interaction of genetic and environmental factors seems to be a risk of developing this spectrum of diseases. The strongest genetic association has been linked with the human leukocyte antigen (HLA) class II alleles, especially the HLA-DRB1*0301 and DQA1*0501. Viral infections such as coxsackie, echo and influenza viruses are some environmental factors associated with IM. Other environmental factors include exposure to ultraviolet (UV) light. Several drugs may induce myopathies mimicking IM. The most common drugs implicated are statins. Other drugs are cimetidine, chloroquine, colchicine and others.

The adaptive and the innate immunity are involved in disease pathogenesis. Cytokines, complement, T and B cells as well as macrophages are involved in the pathogenetic mechanisms of IM.

9.3 Epidemiology

IM are rare disorders and for that reason robust epidemiological studies are lacking. Nevertheless, the incidence for IM comprises between 2.18 and 7.6/million/year with some authors estimating that IM can be as high as 10.1/million/year. The prevalence ranges from 2.4 to 11.49 cases/100000 inhabitants. The age of patients with IM varied from 40 to 55 years. IM present a first peak during childhood and a second during adulthood. Female patients are more prone of developing IM than males. The incidence of DM varies in different countries with different climates leading to the conclusion that UV radiation intensity may play a role.

9.4 Signs and Symptoms

IM share some common clinical features but they also may present with some different clinical patterns.

Dermatomyositis (DM) is the most common subtype of the IM. Skin manifestations are characteristic for the disease and can precede or accompany muscle weakness affecting mainly the proximal muscles. Periorbital heliotrope rash with or without oedema, erythematous rashes on different anatomical regions such as the face, knees, elbows, malleoli, neck, anterior chest (known also as V-sign), back, and shoulders (known also as shawl sign) are not uncommon. Gottron's papules another characteristic feature of DM consists of violaceous eruptions on the knuckles. Other skin manifestations including irregular and thickened cuticles of the fingernails and cracked palmar fingertips (known also as mechanic's hands) are highly characteristic of the disease. Calcifications are another striking feature of DM with slow progression, usually debilitating effects and poor quality of life. When a patient presents with the above signs but there is no muscle involvement, then the term "amyopathic DM" or DSM is applied. Patients with DM appear to have a very high risk for cancers (ovarian cancer, breast cancer, colon cancer, melanoma, non-Hodgkin's lymphoma). In addition, DM may appear as a paraneoplastic syndrome.

Polymyositis (PM) is rare and usually it is a diagnosis of exclusion. By definition, the patient must not have any skin manifestations but a subacute proximal myopathy pattern excluding also other neuromuscular diseases or exposure to specific drugs.

Necrotising autoimmune myositis (NAM) occurs more frequently than PM. The onset can be acute or subacute and the characteristic of the disease is the very high creatine kinase (CK) levels, which can be more than fifty times the upper limit of normal (ULN) in early active disease. It can appear after viral infections, cancer, and connective-tissue disorders or in patients taking statins but it may also occur with no obvious reason. In these cases, the presence of antibodies against 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the enzyme that statins are targeting, is highly diagnostic.

Inclusion-body myositis (IBM) is the most common form of myopathy after the age of fifty affecting mostly males. The onset of the disease is typically insidious and can be misdiagnosed as PM, but later, when there is no response to treatment the correct diagnosis is sought. It is the sole subtype that can present distal muscle weakness. Camptocormia or head drop are two striking features of the disease.

9.5 Diagnostic Modalities

Clinical examination and history are the mainstays for a correct diagnostic outcome. Especially in DM where skin manifestations are usually the first sign of the disease. The pattern of muscle weakness is also of particular importance. Nevertheless, the clinical suspected diagnosis of IM is confirmed by examination of serum muscle enzymes, especially CK, electromyography (EMG) findings and muscle biopsy.

Electromyography: when there is strong suspicion of a IM subtype, EMG is diagnostically useful. It can also rule out other conditions such as neurogenic disorders and lead the physician to the correct diagnosis. It is not a disease-specific modality as the results may be the same for the different subtypes (e.g. active and chronic myopathic units may be seen in DM, PM but also in IBM).

Imaging: plain radiography does not have a major role as a diagnostic tool in IM, but it can assess the progression of calcifications, or lung involvement. In addition, magnetic resonance imaging (MRI) is highly helpful showing muscle oedema or myofascitis or in case of IBM atrophy of the affected muscles. It can also be used as a guide tool for the appropriate biopsy site. Computed Tomography (CT) can be used especially in patients with pulmonary involvement.

Biopsy: muscle biopsy is of utmost importance as it can point out the correct diagnosis with specific patterns for every IM subtype and rule out other conditions, provided that the correct specimen has been studied.

Laboratory: a high serum CK in the appropriate clinical context may point to the diagnosis of an IM. Although all subtypes of IM have an elevated CK, patients with

IBM have the lowest ($<10\times$ ULN) whereas patients with NAM have the highest values ($>50\times$ ULN). Aldolase is elevated and always should be investigated. Liver enzymes, (aspartate aminotransferase – AST and alanine aminotransferase – ALT) may be elevated and should not create confusion to the clinician as regarding liver pathology.

Autoantibodies are a fundamental diagnostic tool for IM. Autoantibodies are detected in about 60% of patients with IM. Myositis specific autoantibodies (MSAs) are highly selective and directed against cytoplasmic or nuclear components of the cell. The three best characterised antibody specificities target mainly the cytoplasmic enzymes (anti-aminoacyl-tRNA synthetase, ARS), the nuclear helicase protein Mi-2 and the cytoplasmic complex signal recognition particle (SRP). Moreover, several new autoantibodies have been recently described. Anti-ARS antibodies are the most prevalent MSAs found in 25–35% of cases. Anti Jo-1 is the most common among them, found in 20–30% of patients with DM and 60–70% of patients with interstitial lung disease (ILD). Anti-ARS antibodies and especially anti-Jo-1 is associated with antisynthetase syndrome (ASS) characterised by ILD, non-erosive arthritis, Raynaud's phenomenon (RP), mechanic hands, skin rashes and fever. *Anti-SRP* and *anti-HMGCR* are specific for NAM. *Anti-NT5C1A* is associated with IBM. *Anti-MDA-5* is associated with DM sine myositis.

9.6 Management

Lifestyle: patients must find the proper exercise programme for them that will strengthen muscles and muscle groups not affected by their disease process, while protecting the muscles that are affected. In this way, the body will be better able to compensate for the weakness. A professional physiotherapist will assist those patients with the correct exercises.

Medical Treatment: corticosteroids (CS) are the first-line treatment for IM except IBM. For mild cases, oral prednisone can be administered as the sole treatment. More severe cases or those with no response to oral treatment should have intravenous administration and CS-sparing agents thereafter [e.g. methotrexate (MTX), azathioprine (AZA)]. In refractory cases, intravenous immunoglobulins (IVIG) have proved effective. In contrary, IBM, possible because of the long-term insidious character of the disease, does not respond to the above treatment schemes. IVIGs have shown some improvement in some of the patients but with disappointing results overall.

Surgical Treatment: small calcifications can be rejected surgically in some cases. In addition, for life-threatening cases of dysphagia cricopharyngeal dilation or myotomy may be considered.



Fig. 9.1 Gotttron's papules (collodion patches)

Gotttron's papules are erythematous to violaceous and sometimes scaly bumps that erupt on any of the metacarpophalangeal (MCP) or interphalangeal (IP) joints (knuckles). These papules can also be present on the knees or the elbows of the patient. In Fig. 9.1a, Gotttron's papules are more prominent on the 2nd–5th MCPs and proximal interphalangeals (PIPs) on both hands (yellow arrows). The same patient had also mild RP (Fig. 9.1b), which is a common finding in DM patients (white arrows). In Fig. 9.1c another example is shown.



Fig. 9.2 Gottron's sign

Gottron's papules and Gottron's sign are two terms that are used interchangeably by some authors. Gottron's papules are discussed in Fig. 9.1 of this chapter. Gottron's sign has the same distribution but it is flat (Fig. 9.2a). It is a distinct cutaneous finding consisting of erythematous to violaceous macules (it is not palpable). Both findings are considered pathognomonic for DM and can be found on the skin of the same patient.

Figure 9.2b shows a patient with Gottron's sign on both knees.

Figure 9.2c shows a patient with Gottron's sign on the elbow. Figure 9.2d depicts a rare finding. Gottron's papules and sign are usually seen on the dorsal surface of the hand, but rarely, these findings can also be present on the palmar aspect and should be differentiated from vasculitis.





Fig. 9.4 Periorbital heliotrope rash and other facial rashes of dermatomyositis

Heliotrope rash may be the first sign of DM (Fig. 9.4a, b). It is an erythematous or bluish-purple rash that develops on both eyelids and can be associated with oedema (Fig. 9.4b, c). The name “heliotrope rash” comes from the flower *Heliotropium peruvianum*, which has small purple petals. As you can notice, there may also be a “butterfly” distribution across the bridge of the nose and upper cheeks, which reflects light exposure and may lead to confusion with SLE (Fig. 9.4a). The above figures depict the expression of facial rashes on different patients. It has to be differentiated with Jellinek’s sign seen in hyperthyroidism (pigmentation of the eyelids).

Fig. 9.3 “Mechanic’s hands”

Patients suffering from DM or PM may develop a roughening and cracking of the skin of the fingers (usually at the tips and sides of the fingers) resulting in irregular, dirty-appearing lines that resemble those of a manual laborer (Fig. 9.3a–c). This sign has been considered for a long time a characteristic skin finding of DM, but it has been reported as a finding also in collagen vascular-related interstitial pneumonia, SLE and mixed connective tissue disease (MCTD). These figures are from a female patient diagnosed with DM.



Fig. 9.5 Unilateral heliotrope rash

Rarely, the heliotrope rash is unilateral or more prominent on one side. In that case, the differential diagnosis of eyelid erythema and oedema is broad, ranging from benign, self-limiting dermatoses to malignant tumors and vision-threatening infections. It can be also a sign of IgG4-related disease. The clinician should rule-out severe conditions such as orbital cellulitis, which requires hospitalization and intravenous antibiotics to prevent vision impairment/loss. A detailed physical examination and evaluation of symptoms and exposures can lead the clinician to the correct diagnosis and the appropriate treatment.

In this young lady suffering from DM, a unilateral heliotrope rash is evident in the right eyelid.



Fig. 9.6 V-sign or V-neck sign

The V-sign is a widespread, flat, erythematous to violaceous area that appears on the front of the chest and particularly in the area of skin exposed by a V-necked sweater. It can worsen with exposure to ultraviolet light.

The extension of this sign as well as the discoloration of the skin may vary.

Figure 9.6a–e, show different patients with DM and the V-sign.

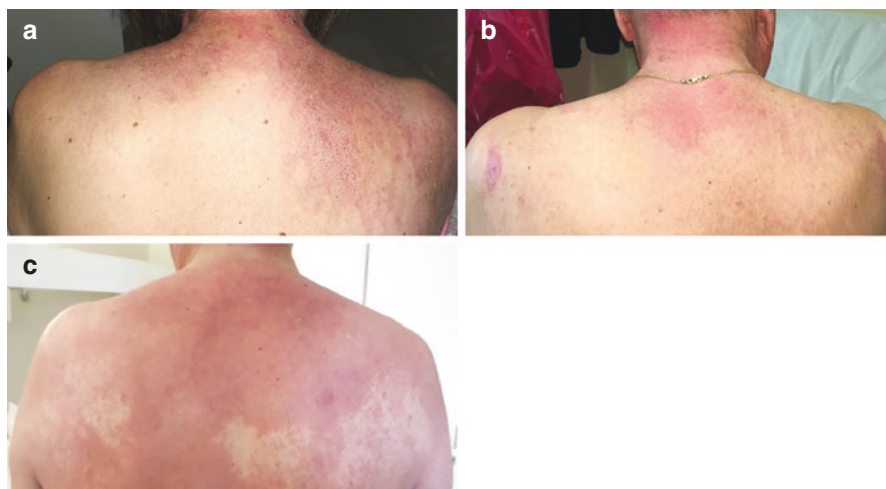


Fig. 9.7 Shawl sign

The shawl sign has an appearance similar to that of the V-sign but appears on the upper back, shoulders, and at the back of the neck. Figure 9.7a–c show different patients with DM. The shawl sign as well as skin discoloration is evident.

Fig. 9.8 Holster sign of dermatomyositis

Another skin manifestation of DM is the so-called “holster-sign”. It is a confluent, macular, violaceous erythema present on the lateral side of hip and thighs as depicted in these two patients diagnosed with DM.

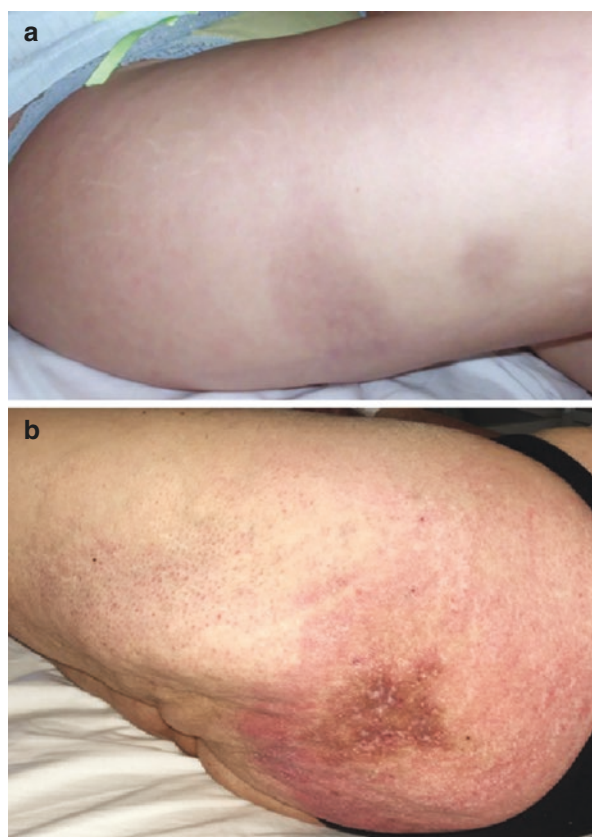




Fig. 9.9 Poikiloderma vasculare atrophicans

Poikiloderma vasculare atrophicans is a cutaneous condition which can be seen in DM patients but also in other conditions such as skin lymphomas and SLE or it can be idiopathic. The affected skin appears hypo- or hyperpigmented with telangiectatic lesions and skin atrophy. Sometimes, this condition is referred to as parapsoriasis variegata or parapsoriasis lichenoides.

This male patient suffers from DM and extensive poikiloderma skin lesions affect the upper back and shoulders.

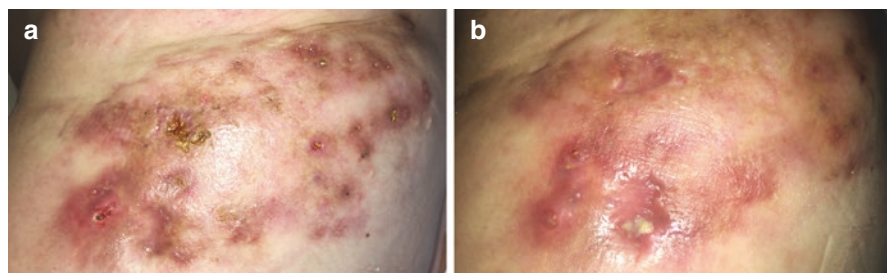


Fig. 9.10 Calcinosis in dermatomyositis

Calcinosis cutis develops more frequently in children but adults are also affected. It is a complication of DM, difficult to treat and potentially disabling. Calcinotic deposits are often located around areas that experience frequent trauma, but any area can be affected. They can ulcerate and a chalky discharge may appear. There is not a definite cure. Sometimes surgical removal can be applied, but when muscles are also involved or the calcinosis is widespread, then conservative treatment is required.

Here, they are visible at the lateral aspect of the gluteal region. You can notice the ulceration of the skin (Fig. 9.10a, b). On physical examination, the skin is taut and a firm, non-mobile, tender subcutaneous plaque can be palpated. This patient had frequent hospitalizations due to recurrent infections of the skin. Figure 9.10b shows the same patient 6 months after initial treatment with antibiotics and topical creams. Figure 9.10c–e show the extension of the calcifications with CT imaging (white arrows).

Figure 9.10f shows the initial presentation approximately 14 years ago.

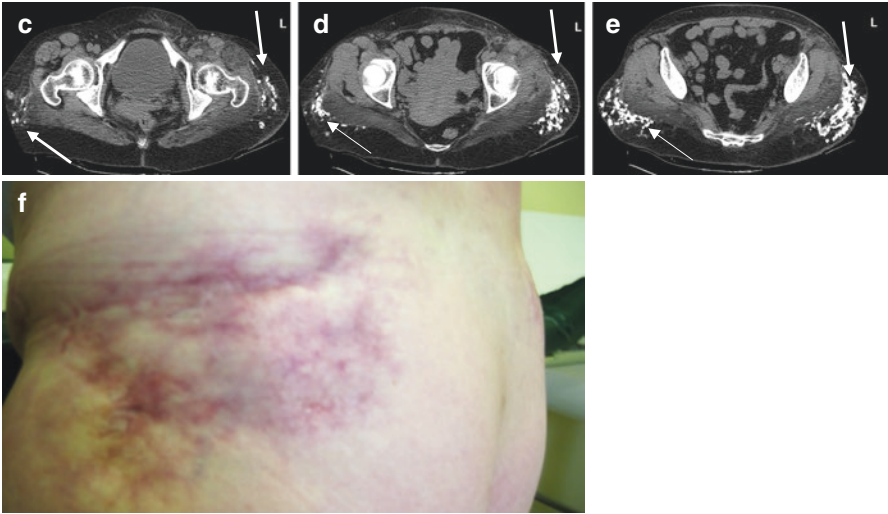


Fig. 9.10 (continued)





Fig. 9.12 Ear calcinosis

As mentioned in Fig. 9.10, calcinosis develops more frequently in younger patients. This 23-years old patient has been diagnosed with juvenile DM since the age 14. He developed calcinotic deposits with vasculitic changes on both helices of the ears (Fig. 9.12a–d). It is not a typical finding, but clinicians should always bear in mind that these deposits can appear on any surface under the skin.

Fig. 9.11 Dermatomyositis with subcutaneous calcific deposits and lipodystrophy

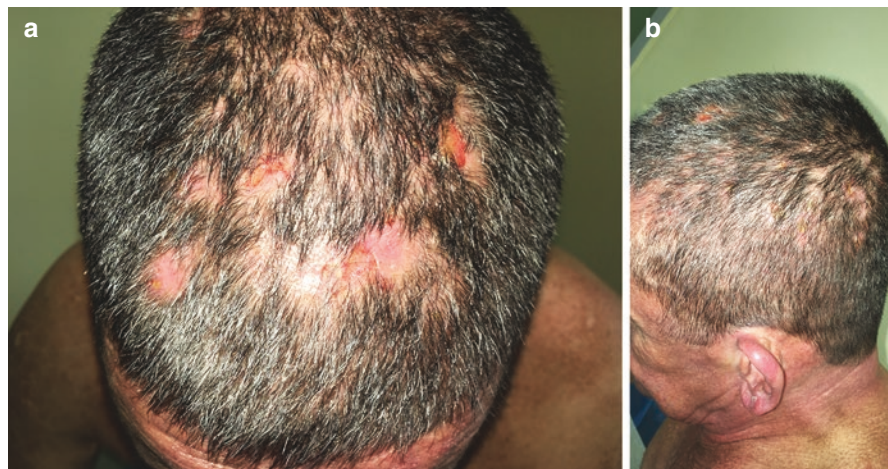
Lipodystrophies represent a heterogeneous group of diseases characterised by altered body fat repartition. It can be associated with metabolic disorders and autoimmune diseases, primarily juvenile DM. Lipodystrophies can occur in generalised, partial, or localised form. Lipodystrophy in association with adult-onset DM, however, is very rare.

This patient had been diagnosed with DM. Several years after the diagnosis, the patient developed calcific deposits under the skin and some lipodystrophic areas around the calcifications. In Fig. 9.11a, a general view of the three calcifications can be seen easily (black arrows). Figure 9.11b–e show the lipodystrophic changes in detail (yellow dashed circle demarcates the lesion on the anterior view).

Another patient with DM and generalised, profound lipodystrophic changes affecting the left arm (Fig. 9.11f). In contrary, on the right arm there are extensive calcific deposits (calcinosis cutis) and features of lipodystrophy (Fig. 9.11g). The abdomen, is affected with both calcific deposits as well as lipodystrophic changes (Fig. 9.11h).

Fig. 9.13 Vasculitis

The same patient, as in Fig. 9.12 with vasculitic changes at the tips of his toes which is another feature of DM and should be differentiated by digital skin ulcers observed in SCL patients and vasculitic lesions of SLE, RA and systemic vasculitides.

**Fig. 9.14** Folliculitis decalvans

Folliculitis decalvans is a rare variant of primary cicatricial alopecia. This term is usually used by the authors to underline the inflammatory component of this manifestation. Its aetiopathogenesis remains unclear. *Staphylococcus aureus* seems to play important role in the pathogenesis as it can be isolated in most of the cases. It has been suggested that superantigens or cytotoxins that bind to HLA class II molecules may stimulate T cells. Numerous disorders may cause cicatricial alopecia when localised on the scalp. Chronic discoid lupus erythematosus, lichen planus, SCL, cicatricial pemphigoid, porphyria cutanea tarda and DM are some of those.

Every area of the scalp can be involved but commonly the vertex and occipital areas are predominantly affected. Initial lesions appear as erythematous follicular papules. Later on, pustules and development of scarred areas occur. The lesions are painful and patients are complaining about a burning sensation of the lesions. When disease progresses, white or less pigmented patches of cicatricial alopecia develop. This is a male patient suffering from DM who developed folliculitis decalvans.



Fig. 9.15 A case of dermatomyositis before and after treatment

This 57-year old patient presented to our department with proximal muscle weakness and severe and extensive skin manifestations due to DM. The skin manifestations included face erythema and heliotrope rash affecting the front of the chest (V-sign), the back of the neck (Shawl sign), hands (Gotttron's sign) and thighs (Holster sign). The patient has been treated with IVIG for 6 months. After the third IVIG a significant improvement was noticed regarding the above-mentioned manifestations. On the left you can see the cutaneous findings before treatment while on the right, the figures show the results after treatment.



Fig. 9.16 Dermatomyositis as a paraneoplastic syndrome

DM presenting as a paraneoplastic syndrome due to underlying breast cancer. This patient was living in a rural area and never had a mammogram in the past. Her relatives brought her with difficulty in swallowing, intense muscle weakness and muscle aches. DM is a rare disease and the diagnosis in an adult should raise suspicion of an underlying malignancy. Figure 9.16a, b show the characteristic heliotrope rash. Figure 9.16c, d show cuticular overgrowth, and periungual erythema (ragged cuticles with nailfold telangiectasias).



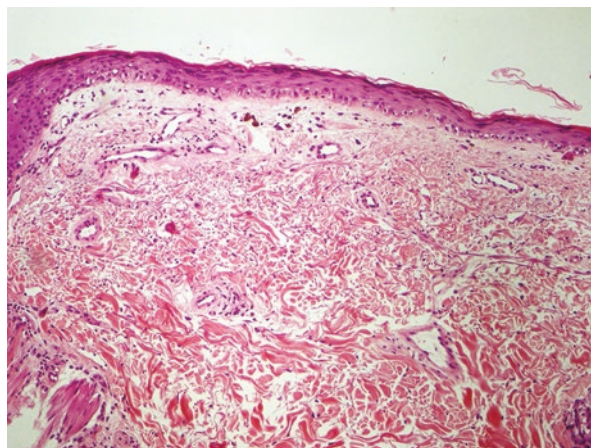
Fig. 9.17 Merkel cell carcinoma

It is well-known that the risk of cancer in patients with classic DM is high. For this reason, health-care professionals should perform a full skin examination at the time of diagnosis and every follow-up visit. Merkel cell carcinoma is a rapidly growing asymptomatic solitary, firm, non-tender, flesh-coloured to red tumour. Clinical unfavourable factors are male gender, localised to head and neck, size of the primary tumour and the presence of immunosuppression. This is a patient with DM. The diagnosis has been made with histologic confirmation and should be performed in all clinically suspicious lesions.

Fig. 9.18

Dermatomyositis – histology

Epidermis focally thin, smudged appearance of the dermoepidermal junction, sprinkling of lymphocytes along the junction, some melanophages and telangiectasias in the papillary dermis. Abundant mucin in the reticular dermis (H/E, $\times 100$).



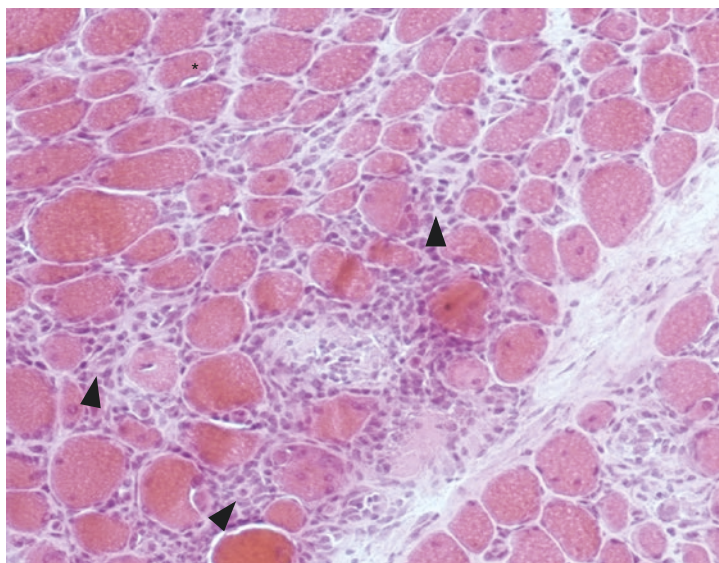


Fig. 9.19 Polymyositis – histology

Muscle biopsy from a patient with PM (Hematoxylin & Eosin). The muscle biopsy shows endomysial inflammatory infiltrates (black arrowheads) and increased variability of fiber size.

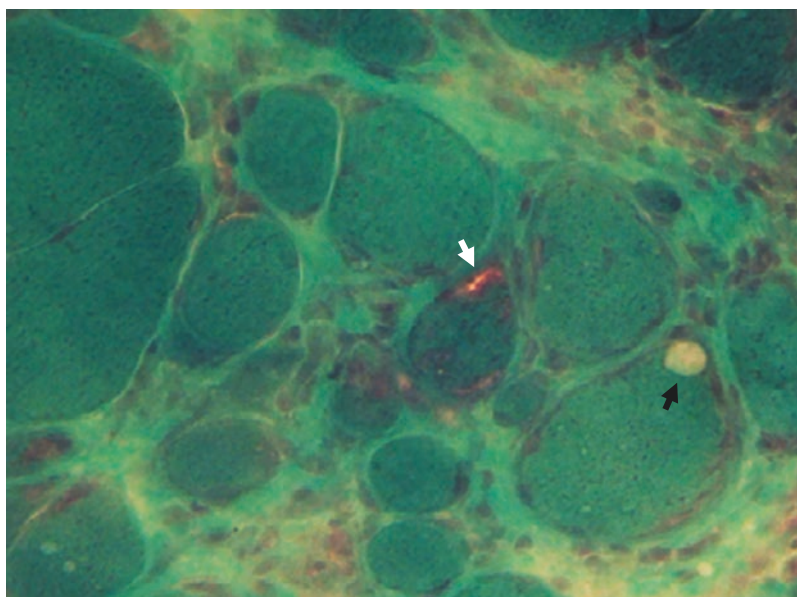


Fig. 9.20 Inclusion body myositis – histology

Muscle biopsy from a patient with IBM (modified Gomori trichrome). The muscle biopsy shows pronounced variation in fiber size, inflammatory response and a fiber with a rimmed vacuole (black arrow). Note also a ragged-red fiber (white arrow).

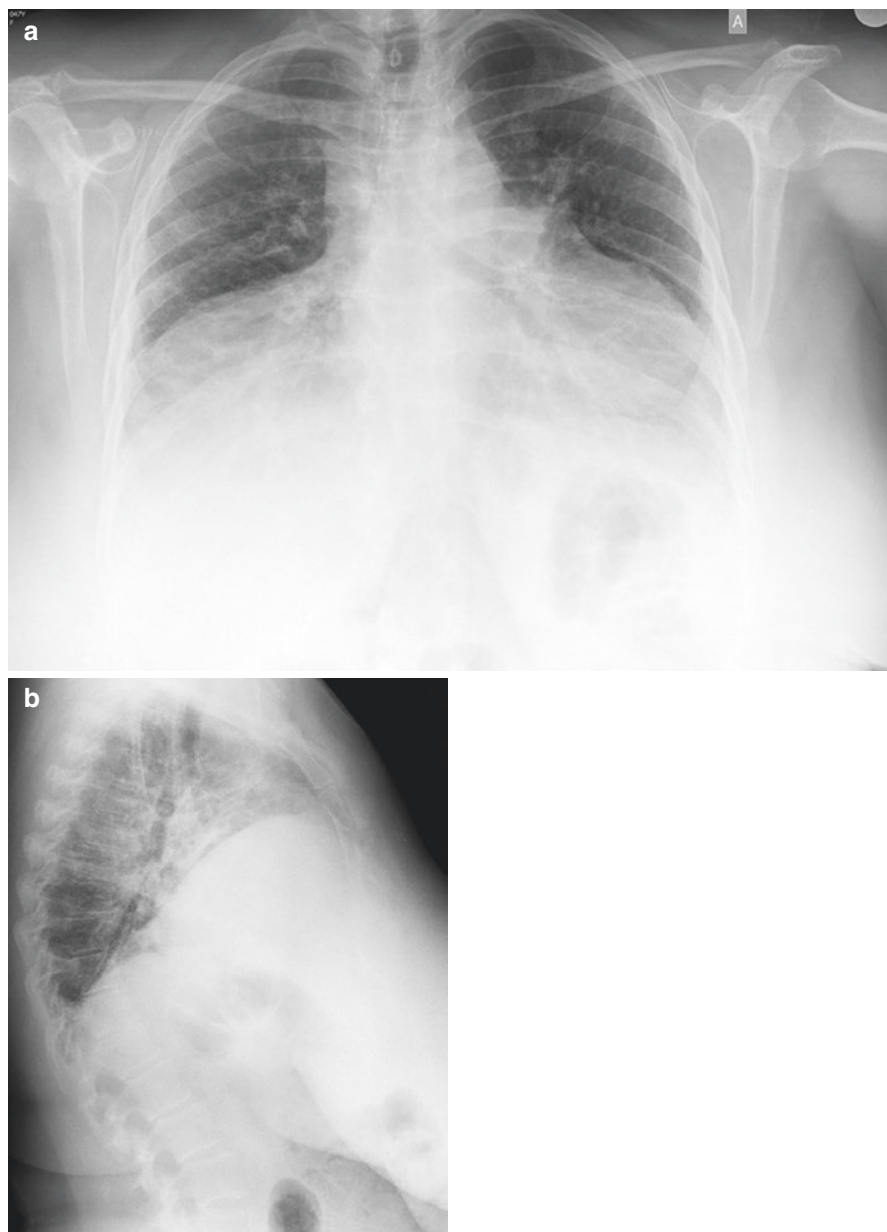


Fig. 9.21 Polymyositis – lung involvement (plain radiography)

PM, except the musculoskeletal manifestations can also affect other organs, especially the lungs, either primarily or through complications of muscle weakness, resulting in ILD, ventilatory insufficiency, and aspiration pneumonia. Patients with positive anti-Jo-1 antibodies are in higher risk of developing severe lung involvement. These are plain radiographs of a 49-years old female patient with PM and positive anti-Jo-1 antibodies. Note the restriction of the lung parenchyma with fibrotic appearance. This patient is on 24-h oxygen therapy at home.



Fig. 9.22 Polymyositis – lung involvement (computed tomography)

High resolution computed tomography (HRCT) scanning of the lungs is a sensitive test, by accurately demonstrating evidence of ILD changes. Plain radiography is of inferior diagnostic importance. In this HRCT lower lobe fibrosis is evident with ground-glass opacities. In general, in PM but also DM with ILD, the more common HRCT abnormalities are linear opacities, irregularity of the interfaces, and ground-glass opacities. Honeycombing and bronchiectases tend to be rarer.

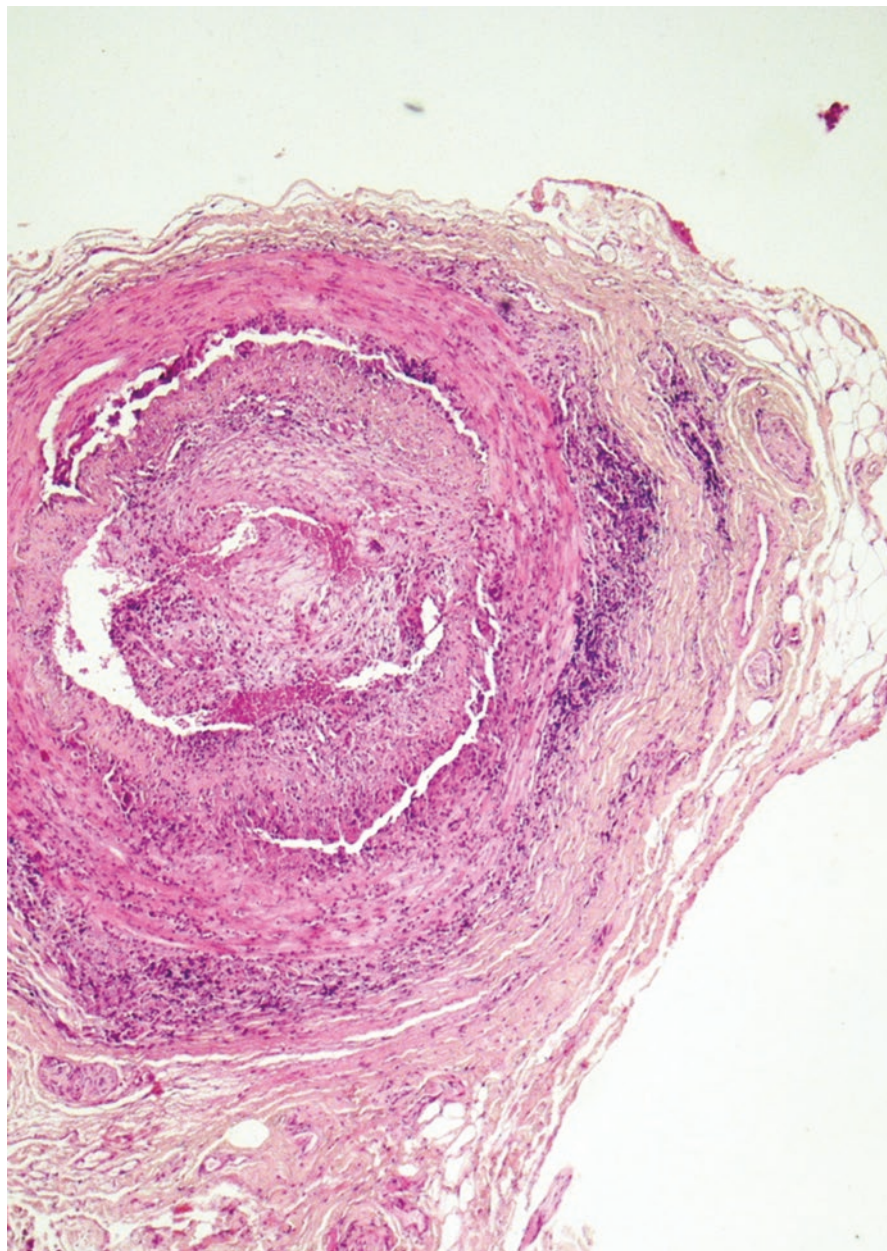
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Chapter 10

Vasculitides



10.1 Introduction

Vasculitis is the umbrella term for a spectrum of heterogeneous inflammatory vascular diseases. Due to a considerable overlap between different types of diseases, in 1992 the Chapel Hill consensus conference introduced a general classification according to the size of the involved vessels, differentiating between large, medium size and small vessel diseases. In 2012, the revised international Chapel Hill consensus conference was convened to improve the nomenclature, change names and definitions as appropriate, giving emphasis on making changes only when justified.

10.2 Aetiology and Pathogenesis

The aetiology as well as the pathogenetic mechanisms are uncertain, but some forms of vasculitis seem to have a link with viral agents such as some forms of polyarteritis nodosa (PAN) (linked to hepatitis B) and cryoglobulinaemic vasculitis (linked to hepatitis C). The above associations led to a better understanding of the pathogenetic mechanisms yet more research needed in order to elucidate the exact pathogenetic pathways. It is generally considered that a complex interaction takes place between an environmental trigger factor (e.g., drugs, chemicals, infection, smoking) and a genetically predisposed host.

10.3 Epidemiology

Giant cell arteritis (GCA) is the commonest form of systemic vasculitis with an age-specific increase in incidence with a peak incidence to those aged over 80 years. Takayasu's arteritis (TA) has a relatively uniform global incidence of 1–2/million. The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) have an overall incidence of 20/million. Henoch-Schönlein purpura (HSP) is the commonest form of childhood vasculitis in the West with an incidence of 20/100,000 aged <17 years but adults can also be affected. Behçet's disease occurs along the Silk Road with a prevalence that reaches up to 380/100,000 in Turkey.

10.4 Nomenclature and Classification

The 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides is the current used. It is neither a classification system that specifies what findings must be observed in a specific patient to classify that patient for clinical research nor a diagnostic system that directs clinical management. The main classification consists of large-vessel vasculitis (TA, GCA), medium-vessel

vasculitis (PAN, Kawasaki disease), small-vessel vasculitis [AAV (microscopic polyangiitis – MPA, granulomatosis with polyangiitis – GPA, eosinophilic granulomatosis with polyangiitis – EGPA), immune-complex small-vessel vasculitis (anti-glomerular basement membrane disease, cryoglobulinaemic vasculitis, HSP, hypocomplementaemic urticarial vasculitis)], variable-vessel vasculitis (Behçet's disease, Cogan's syndrome).

10.5 Signs and Symptoms

The classification and diagnosis of vasculitis is challenging because of the heterogeneous nature of these illnesses. The majority of the patients suffering from a vasculitis syndrome may present with constitutional symptoms like malaise, arthralgias, weakness, low-grade or spiking fever. The clinical features and signs are related to the segment of the affected vessels and the blood supply to the corresponding tissues. They are also related with the degree, extent and the number of vessels involved causing ischaemia and damage of the corresponding organs and tissues. Nevertheless, there are some characteristic features and common presenting features that help the clinicians to distinguish those entities.

Takayasu's arteritis (TA): extremity claudication, arthralgias, constitutional symptoms and granulomatous aorto-arteritis usually occurring before the age of 50.

Giant-cell arteritis (GCA): new-onset headache, polymyalgia rheumatica symptoms, jaw or tongue claudication, scalp tenderness, fever, vision disturbances with granulomatous aorto-arteritis predominantly involving the carotid and vertebral arteries occurring after the age of 50.

Microscopic polyangiitis (MPA): vasculitis of small/medium vessels. ANCA positivity and pauci-immune glomerulonephritis are frequent.

Granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis (WG): recurrent epistaxis or sinusitis, pulmonary infiltrates, pulmonary nodules, glomerulonephritis, ocular involvement. Granulomatous inflammation of the respiratory tract with vasculitis of small/medium vessels. ANCA positivity.

Eosinophilic granulomatosis with polyangiitis (EGPA) or Churg-Strauss syndrome: allergic rhinitis, asthma, eosinophilia, pulmonary infiltrates, coronary arteritis, intestinal ischaemia, vasculitis of small/medium vessels. History of asthma, eosinophilia and eosinophilic granulomatous inflammation involving the respiratory tract. Sometimes positive ANCA.

Cryoglobulinaemic vasculitis: serum cryoglobulins (cryo) positive, skin (palpable purpura), glomerular and peripheral nerve involvement.

Immunoglobulin (Ig) A vasculitis: possible IgA nephropathy, arthritis, frequent skin (palpable purpura) and gastrointestinal vasculitis (intestinal ischaemia) with IgA deposits.

Behçet's disease: recurrent oral and/or genital ulcers with skin, ocular, articular, gastrointestinal, and/or central nervous system lesions. Variable-vessel vasculitis is possible.

10.6 Diagnostic Modalities

The diagnostic work-up should be tailored to the clinical situation and geared toward a tissue or angiographic diagnosis, always bearing in mind that the findings from these studies are not pathognomonic in some cases.

Laboratory: initial investigations include full blood count (FBC), inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), renal function tests. Inflammatory markers provide a non-specific tool for assessing inflammatory activity and monitoring treatment. Urinalysis may reveal proteinuria and haematuria or red cell casts indicating active renal inflammation.

ANCA consist of characteristic autoantibodies that are formed towards enzymes and bactericidal proteins within the cytoplasmic granules of neutrophils and monocytes. They can be used as diagnostic tools in AAVs. They divide into two main classes: c-ANCA and p-ANCA.

Imaging: simple x-rays may be used to characterise organ damage in small vessel vasculitis (usually the lungs). Computed tomography (CT) and magnetic resonance imaging (MRI) scans of the paranasal sinuses demonstrate characteristic features in GPA whereas a high-resolution CT (HRCT) scan of the lungs can provide diagnostic and prognostic information in AAVs. MRI demonstrates early vascular inflammation in TA and GCA. Musculoskeletal ultrasound (MSUS) with colour Doppler (CD) may be used as an adjuvant and a quick method to assess a patient with symptomatology of GCA (characteristic “halo” sign and also stenosis and occlusions as well as wall oedema). Positron emission tomography (PET) scans are used in large vessel inflammation. CT angiography may be used in TA and large vessel vasculitides in general. Angiography can be used in patients with PAN but it has been replaced by alternative non-invasive techniques such as MR angiography, CT and CT angiography to determine the extent of vessel involvement.

Histology: histological examination of biopsy material is useful in confirming a diagnosis in the context of clinical findings and laboratory data and is considered the gold-standard investigation in certain vasculitides (e.g. temporal artery biopsy, renal biopsy in AAVs).

10.7 Management

Initial treatment for most types of systemic vasculitis consists of high-dose corticosteroids (CS), with the addition of immunosuppressive agents in certain patients. For GCA and TA medium to high doses of CS are used, often with the use of immunosuppressive drugs like methotrexate (MTX), azathioprine (AZA) or mycophenolate mofetil (MMF) as a CS sparing agent. For AAV high doses of CS are used in combination with cyclophosphamide (CP), or with the use of MTX, AZA, or MMF. In some cases of MPA, rituximab is used. The same treatment strategies as above, usually are used for the rest of vasculitides.

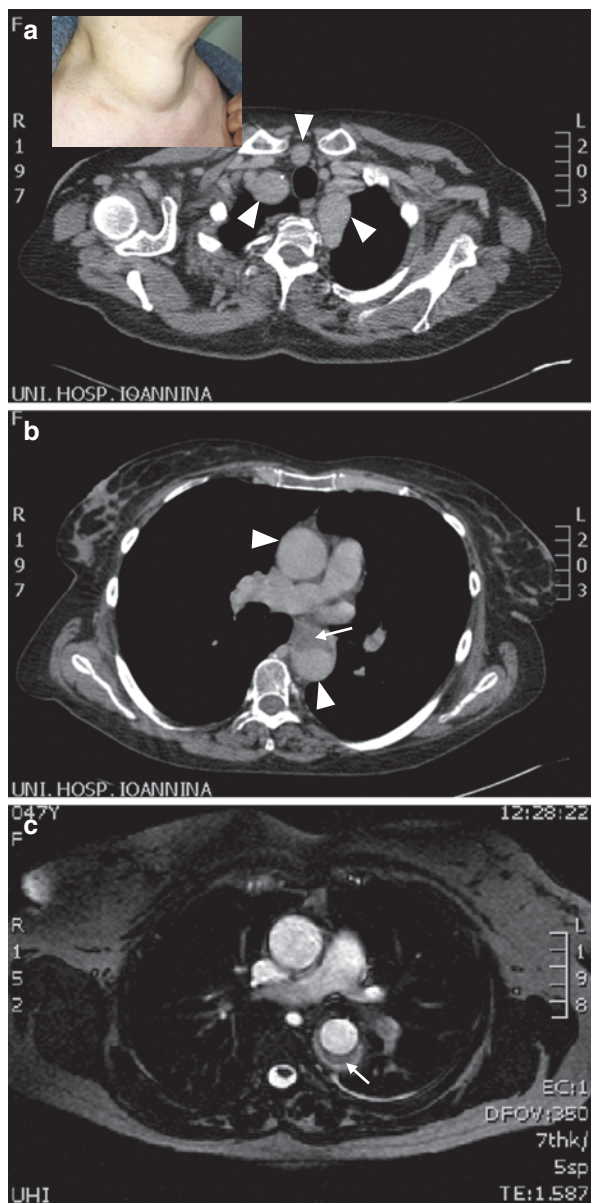


Fig. 10.1 Takayasu arteritis

In Fig. 10.1a and b a CT angiography shows multiple aneurysms at the level of the aortic arch branches as well as the ascending and the descending aorta respectively (white arrowheads). Note the peripheral thrombus formation of the descending aorta (white arrow – Fig. 10.1b). In Fig. 10.1c an MRI angiography of the same patient showing the same vascular findings as in Fig. 10.1b (white arrow).

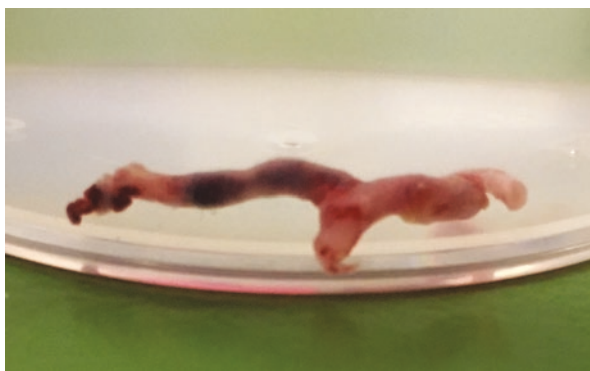
The insert figure in 10.1a shows an enlargement of the anterior part of the neck (masquerading thyroid disease) which corresponds to the aneurysm of the right common carotid artery which was pulsatile and palpable on inspection and palpation.

Fig. 10.2 Giant cell arteritis

GCA is the most common idiopathic systemic vasculitis in persons aged 50 years or greater. This male patient presented with a new-onset headache, mild scalp tenderness and jaw claudication. Note the thickness of his left temporal artery (black arrowheads).

**Fig. 10.3** Giant cell arteritis – biopsy

Temporal artery biopsy specimen. This is the gold-standard method for the diagnosis of GCA. It involves the surgical removal of a small piece of the temporal artery and then sent to the pathologist for careful examination under the microscope (*see next figures for histological findings*).



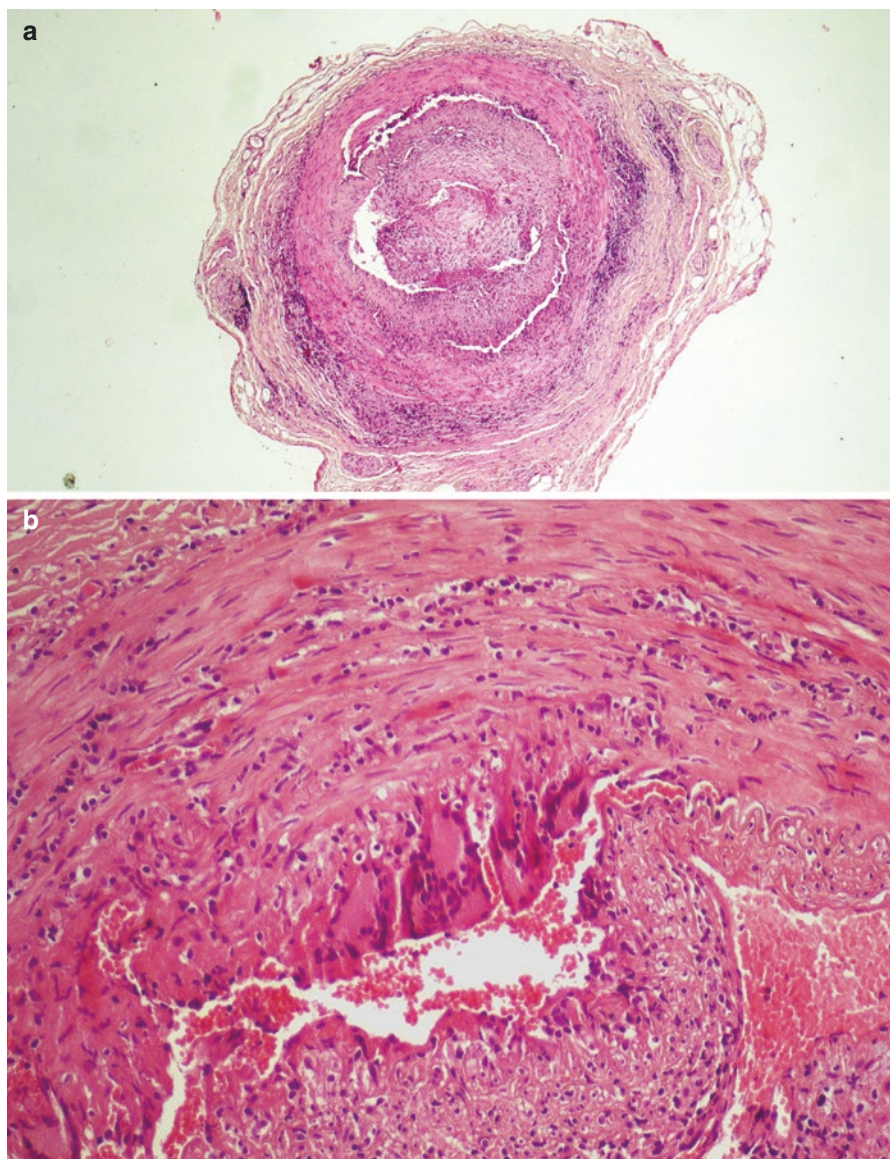


Fig. 10.4 Histologic findings in giant cell arteritis

Histology shows a medium sized temporal artery displaying a heavy inflammatory infiltrate of the wall (Fig. 10.2a H/E ×40) that contains multinucleated giant cells, most of them associated with the elastic lamina (Fig. 10.2b H/E ×200).



Fig. 10.5 Granulomatosis with polyangiitis – saddle nose deformity

A saddle nose deformity refers to a marked depression or collapse along the mid portion of the nasal bridge. GPA or WG is one of the causes that can develop this kind of deformity. Other causes are nasal trauma, congenital syphilis, relapsing polychondritis (RP), cocaine abuse. This 64-years old female was suffering for a long period of time from anosmia due to nasal polyps and recurrent upper respiratory tract infections. CS was the main treatment and this is why you can notice face telangiectasias as well as a cushingoid facies. This is a grade I-II saddle nose deformity (black arrows) in a cANCA – PR3 positive female patient diagnosed as GPA.

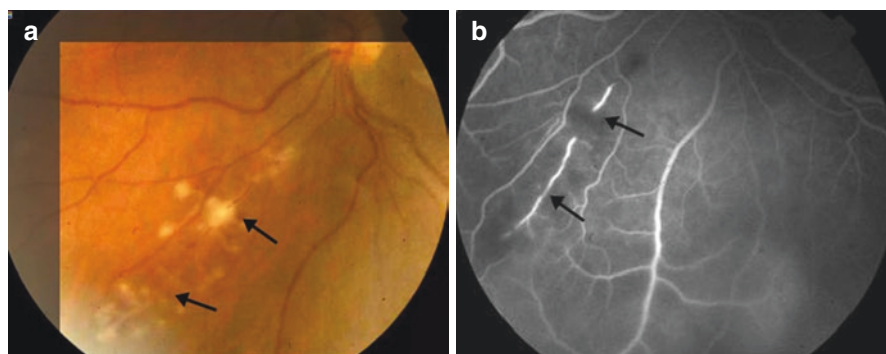


Fig. 10.6 Antineutrophil cytoplasmic antibody – associated vasculitis: ophthalmic complications
Retinal vasculitis (black arrows) in a young man with positive c-ANCA and GPA. Figure 10.6a depicts the fundus. In Fig. 10.6b fluorescein angiography reveals arteritis.

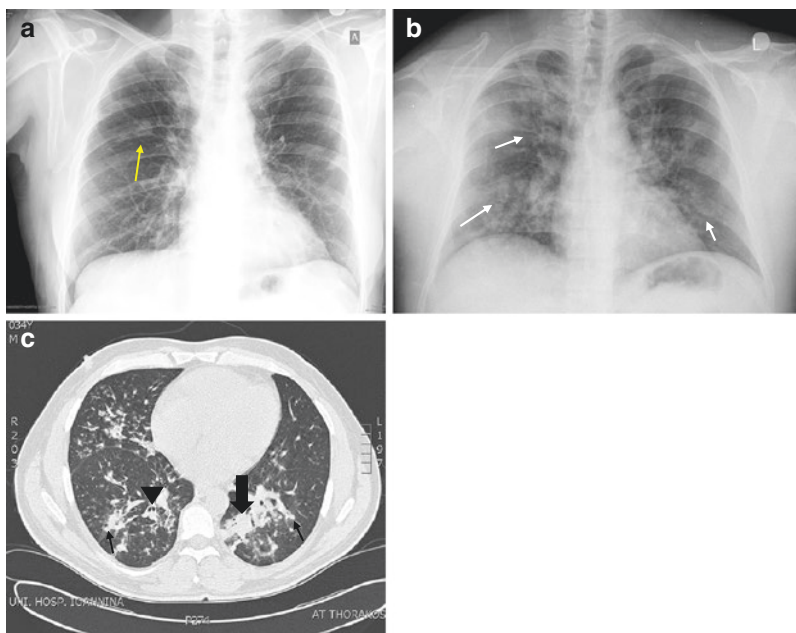


Fig. 10.7 Granulomatosis with polyangiitis – pulmonary involvement

Pulmonary involvement in GPA may be mild/limited or extensive. The radiographic appearances of GPA are widely variable and a diagnosis by imaging alone is difficult. In Fig. 10.7a, a single nodule is located in the right lung (yellow arrow). In Fig. 10.7b and c, more severe pulmonary lesions are depicted on a plain chest x-ray as well as on a CT scan in a 34-years old patient with severe dyspnea and haemoptysis. More specifically, in Fig. 10.7b multiple patchy infiltrates distributed throughout the lungs of variable size are seen. They range from well to poorly defined. A reticulonodular interstitial infiltrate at the bases is also evident. In Fig. 10.7c, nodules and masses (black thick arrow) are seen. Some nodules show halo sign (black arrows). Also note marked bronchial wall thickening in segmental and subsegmental bronchi (black arrowhead). An active diagnostic workup, intensive clinical observation, and aggressive immunosuppressive treatment are cornerstones of the management in such patients. This is a type of diffuse alveolar haemorrhage of a cANCA – PR3 positive patient.



Fig. 10.8 Necrotic vasculitic lesions

Necrotic skin lesions affecting the ankle and foot and purpuric skin lesions affecting the lower leg. This is a 35-year old patient with GPA who presented with high fever, arthralgias and skin lesions. The laboratory evaluation showed an active urine sediment and cANCA PR3 positivity. Renal biopsy is depicted in Fig. 10.9.

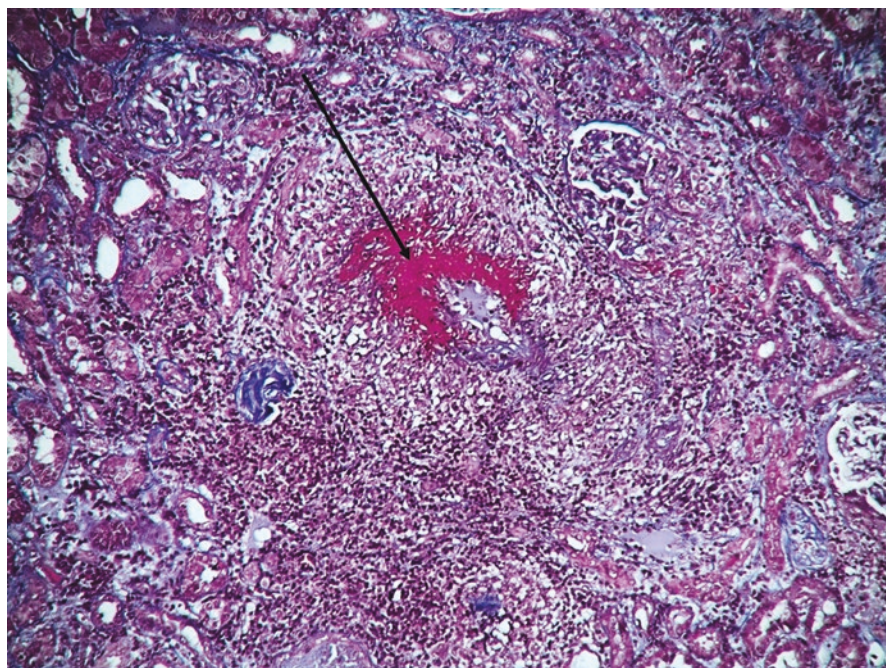
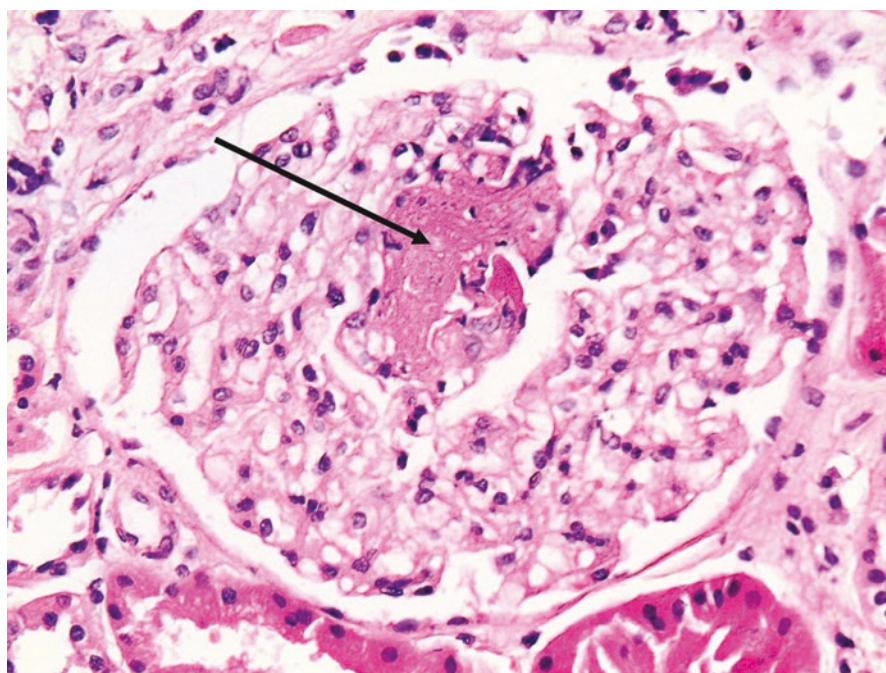


Fig. 10.9 Antineutrophil cytoplasmic antibody – associated vasculitis: renal biopsy of a cANCA vasculitis

Necrotising arteritis: interlobular artery with fibrinoid necrosis of the wall (black arrow). This is a renal biopsy of a patient with a pauci-immune cANCA positive GPA (Masson trichrome $\times 100$).



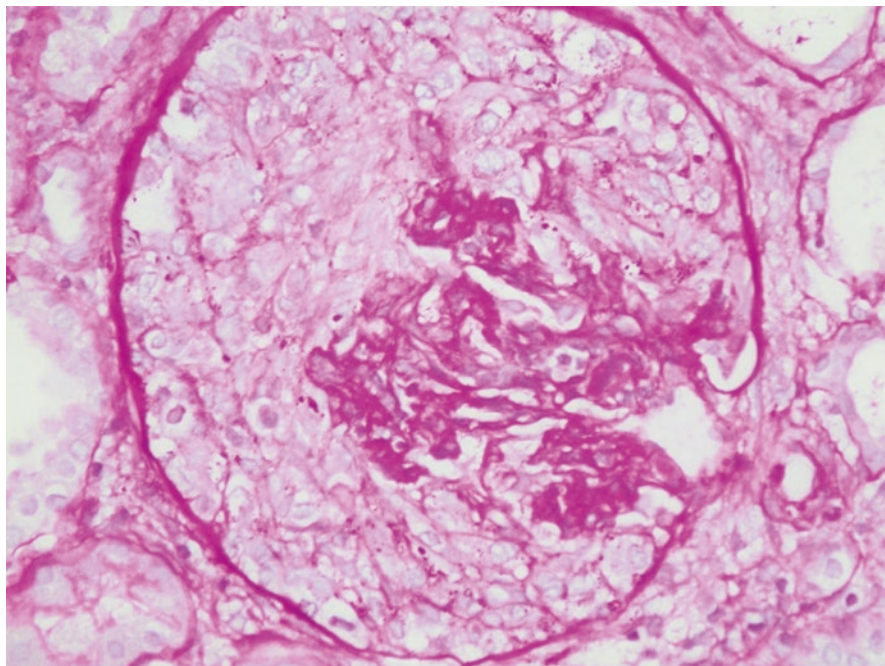


Fig. 10.11 Antineutrophil cytoplasmic antibody – associated vasculitis: renal biopsy of a pANCA vasculitis

Concentric cellular crescent formation consisting of large epithelial cells occupying the Bowman's capsule "strangling" the glomerular loops. This is a renal biopsy of a patient with pauci-immune pANCA positive vasculitis (PAS $\times 400$).



Fig. 10.10 Antineutrophil cytoplasmic antibody – associated vasculitis: renal biopsy of a cANCA vasculitis

Segmental glomerular fibrinoid necrosis (black arrow). This is a renal biopsy of a patient with cANCA positive vasculitis (HE $\times 400$).

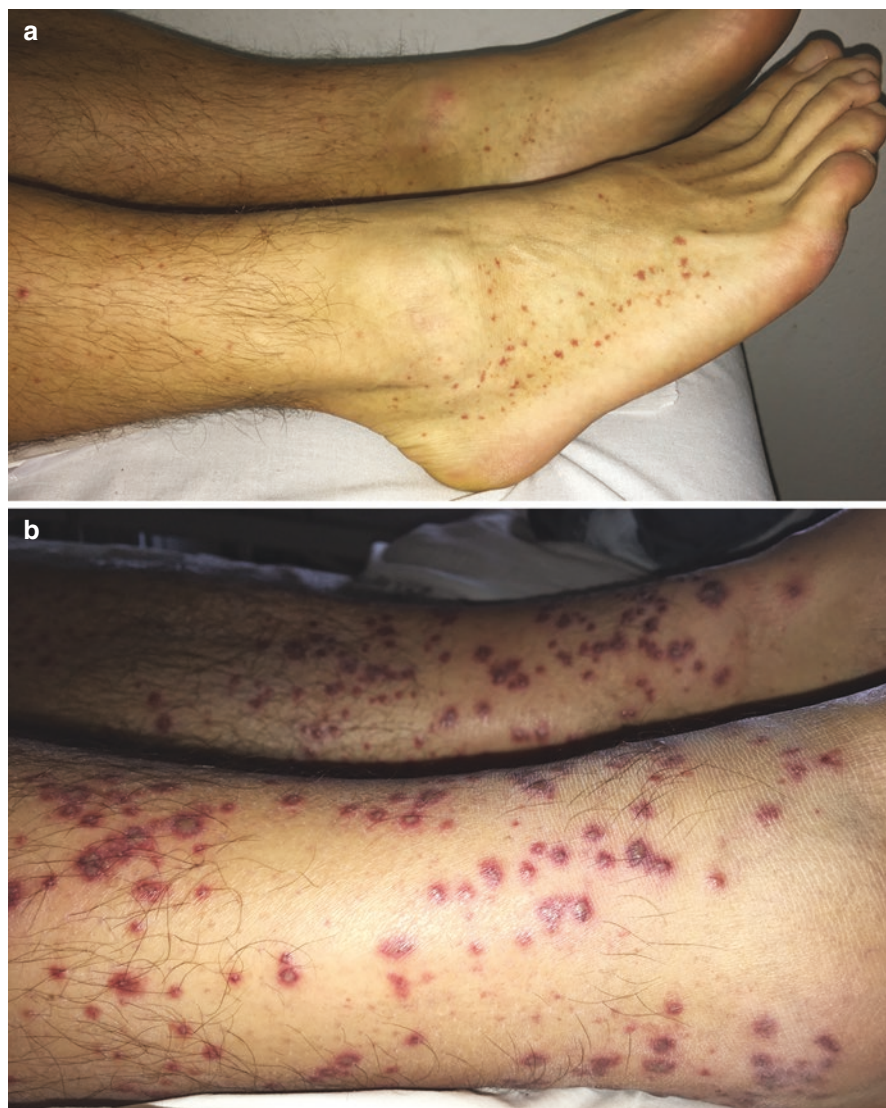


Fig. 10.12 Henoch-Schönlein purpura

HSP is a systemic leukocytoclastic vasculitis often noted as a skin rash with skin lesions such as petechiae (Fig. 10.12a) and palpable purpura (Fig. 10.12b). This is a 35-year old patient with a 2-day history of eruptions on his legs that were mildly pruritic (Fig. 10.12a) and 3 days later the skin lesions became palpable (Fig. 10.12b). The histologic evaluation revealed leukocytoclastic vasculitis (see figure with histology) with IgA immune deposits on the vessel walls. Since HSP may develop complications in adult patients, a thorough investigation should always be performed. Usually a precedent respiratory tract infection may be the cause of this type of vasculitis.

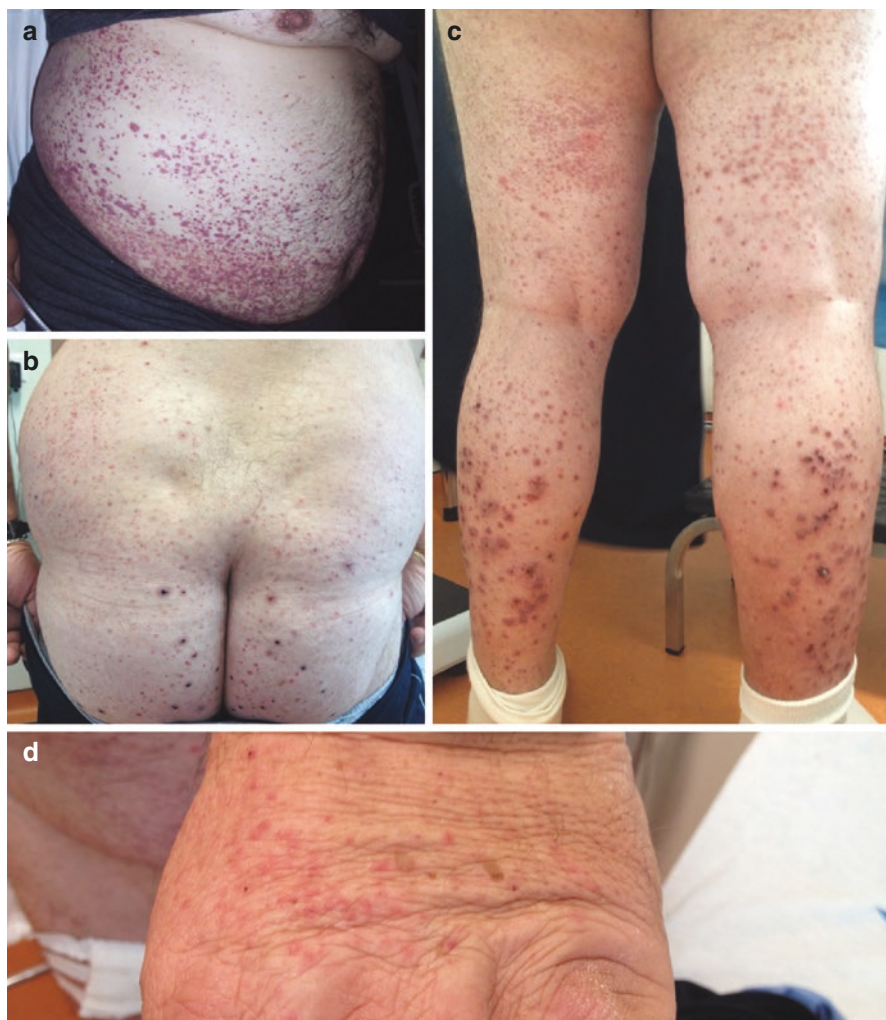


Fig. 10.13 Henoch- Schönlein purpura

Diffuse erythematous palpable purpuric lesions are seen in this patient affecting the lateral abdominal region (Fig. 10.13a), gluteal area (Fig. 10.13b), posterior thighs and calves (Fig. 10.13c) as well as the dorsal surface of the hands (Fig. 10.13d). This is a more generalised form of HSP in a 53-year old adult male. HSP predominantly affects children.

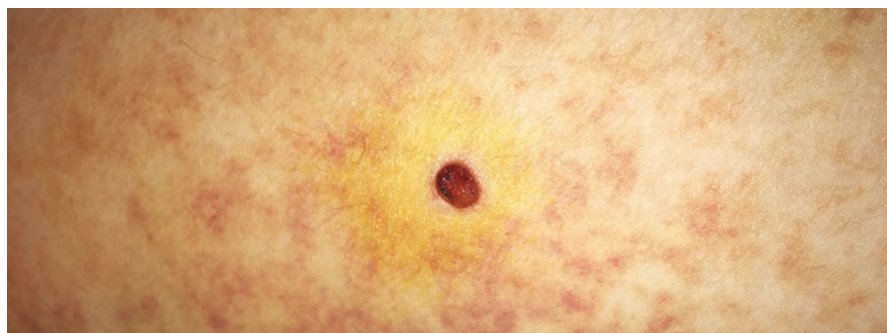


Fig. 10.14 Punch biopsy

Skin biopsy is one of the most important diagnostic tests for skin disorders. Punch biopsy is the most common used technique for the diagnosis of cutaneous vasculitis. Usually, a 3–4 mm cylindrical core of tissue sample is obtained. In Fig. 10.14, an elliptical-shaped wound after the incision is shown.

Fig. 10.15

Leucocytoclastic vasculitis

Figure 10.15a shows oedema of the papillary dermis and moderately perivascular and interstitial infiltrate (H/E, $\times 200$).

Figure 10.15b shows neutrophils and nuclear dust of many neutrophils, extravasated erythrocytes, and fibrin within wall of venules (H/E, $\times 400$).

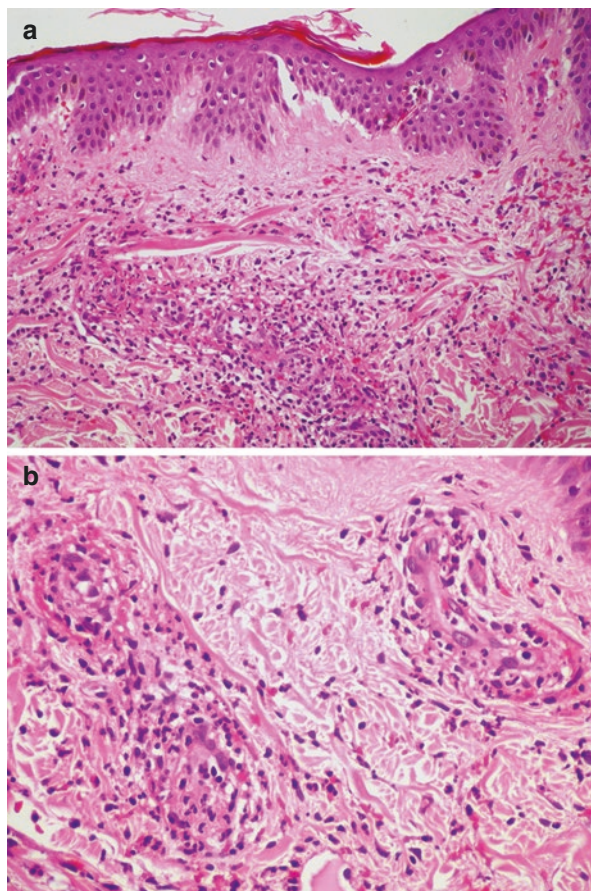




Fig. 10.16 Cryoglobulinaemic vasculitis

Multiple haemorrhagic skin lesions that coalesce on both lower extremities. In addition, purpuric (black arrowheads) and necrotic (black arrows) lesions are also shown in a patient with cryoglobulinaemia due to hepatitis-C infection.

Cryo are proteins that have the potential to precipitate upon exposure to cold. They are thought to represent circulating immune complexes (ICs) and may be associated with many different vasculitic syndromes including AAV, rheumatoid arthritis (RA) vasculitis etc. They may also occur in patients with chronic infections like hepatitis C and B. There are three types of cryoglobulinaemia:

- (a) *type I cryoglobulinaemia or simple cryoglobulinaemia*, is the result of a monoclonal immunoglobulin, usually immunoglobulin M. This type is more frequent in haematological disorders like multiple myeloma, Waldenstrom disease,
- (b) *type II or mixed monoclonal cryoglobulinaemia*, consists of ICs which contain a monoclonal immunoglobulin with RF reactivity and a polyclonal immunoglobulin. This type can be found in haematological disorders as well in patients with systemic lupus erythematosus (SLE), Sjogren's syndrome (SS) and other autoimmune rheumatic diseases (ARDs). Finally,
- (c) *type III or mixed polyclonal cryoglobulinaemia* consists of ICs and contain polyclonal immunoglobulins with RF reactivity.

Types II and III cryoglobulinaemiae represent 80% of all cryoglobulins.



Fig. 10.17 Behçet's disease – oral aphthous ulcer

The main clinical manifestations of Behçet's disease are oral and genital ulcers. Recurrent oral ulceration (minor aphthous, major aphthous, or herpetiform ulceration) is one of the diagnostic criteria for Behçet's disease, followed by genital ulcers, ocular lesions, skin lesions, neurological manifestations, vascular manifestations and positive pathergy test (*see also* Fig. 10.19 *for pathergy test*).

The black arrow shows a minor aphthous lesion of the lower lip in a 35-year old female patient (note also another ulcer on the tip of the tongue – insert picture). Splinter haemorrhages are also visible on both indices and middle fingers of her hands (blue arrows). Finally, oral health is impaired in those patients. Minor spontaneous gum bleeding is also visible (yellow arrows). All the above signs are compatible with Behçet's vasculopathy.



Fig. 10.18 Behçet's disease – pseudofolliculitis

Some patients with Behçet's disease may develop small acneiform eruptions and/or inflammation of the skin such as those depicted in Fig. 10.18. The mean age of development of acneiform lesions is about 30 years. In the suitable clinical context, these eruptions in postadolescent patients with no history of intake of systemic steroids who develop acneiform lesions are considered a sign of Behçet's disease. This is a 32-year old patient diagnosed with Behçet's disease.



Fig. 10.19 Behçet's disease – pathergy test

Pathergy is an exaggerated skin response to injury appearing after minor trauma. It typically occurs in patients with Behçet's disease but it is not a pathognomonic sign. A positive pathergy test is one of the diagnostic criteria for Behçet's disease. It is produced by inserting a 20-gauge needle into the dermis of the forearm of the patients. The reaction is considered positive if a papule or a pustule is formed at the site of the puncture within 24–48 h (left insert picture). Erythema alone is considered negative (right insert picture). Patients with a positive pathergy test are in risk of developing persistent ulceration in severe skin injuries or after a surgical procedure.

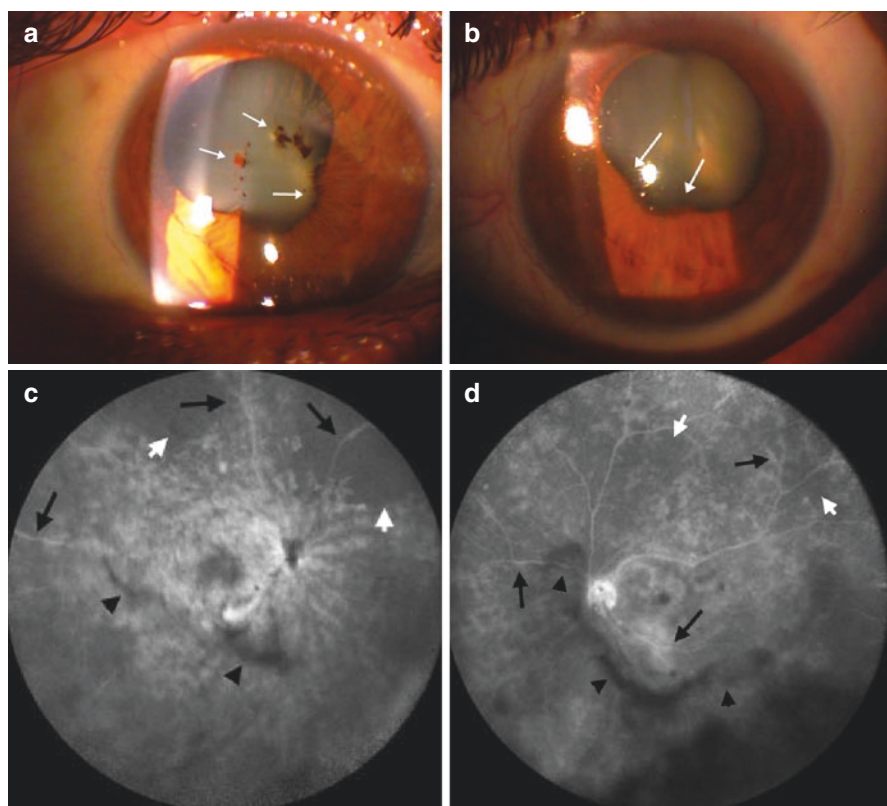


Fig. 10.20 Behçet's disease – ophthalmic complications

Bilateral panuveitis in a man with Behçet's disease.

Figure 10.20a, b involvement of the anterior segment of both eyes (10.20a: right eye, 10.20b: left eye) with irregular pupil due to posterior synechiae (synechiae of iris with crystalloid lens; white arrows).

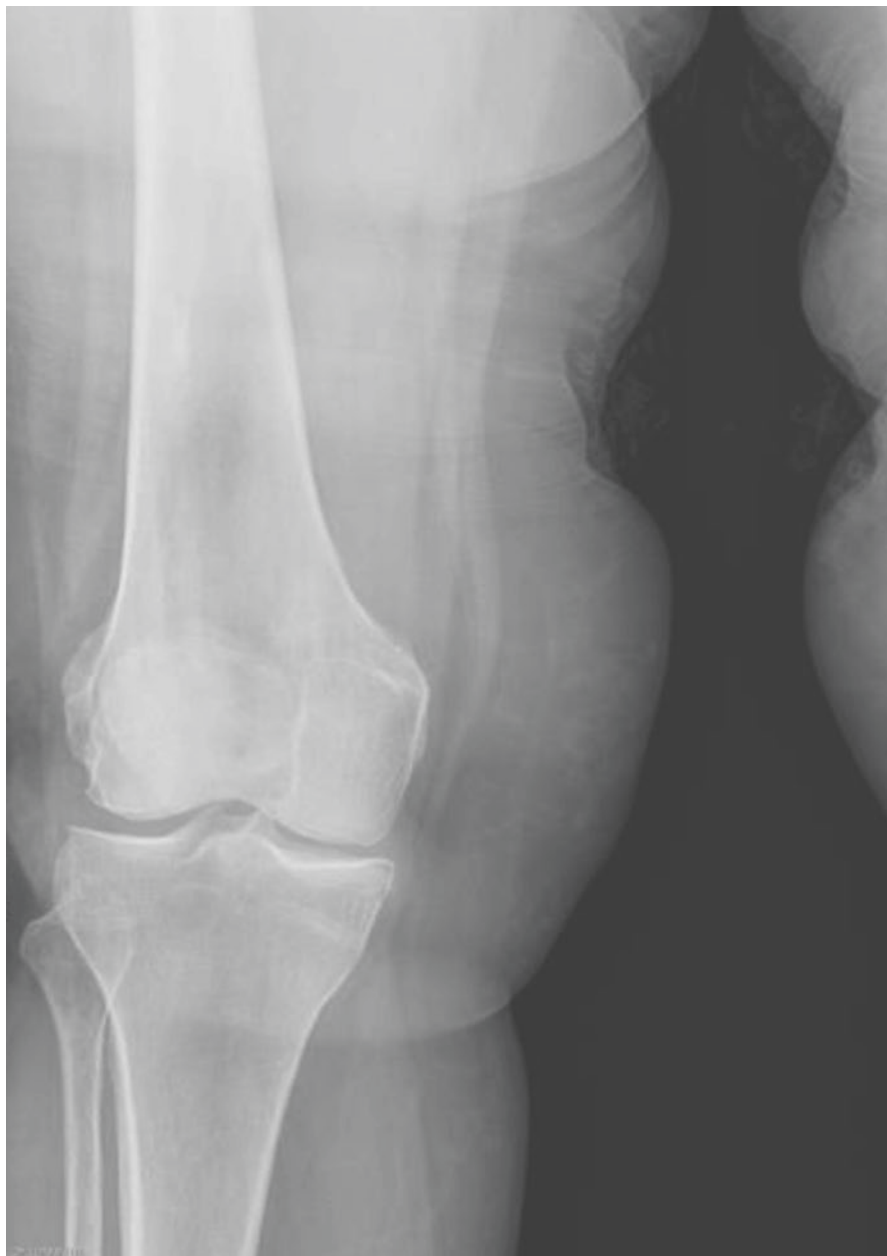
Figure 10.20c, d fluorescein angiography. Involvement of the posterior segment. In both eyes, retinal vasculitis and vitreous inflammation are present (10.20c: right eye, 10.20d: left eye). Retinal vasculitis involves arteries and veins (black arrows) with regions of retinal ischaemia (white arrows). Vitritis is shown by arrowheads (towards the vitreous floaters).

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Chapter 11

Osteoarthritis



11.1 Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide. It is a degenerative chronic condition of the joints that affects all of the weight-bearing components of the joint (articular cartilage, menisci, bone) and most often affects the knees, hips, lower back, neck, small joints of the fingers and the bases of the thumbs and big toe. Risk factors for OA are: age (strongest risk factor), female gender, joint alignment, hereditary gene defects, joint injury, overuse syndromes and obesity. Usually, OA is the result from wear and tear of the joint. The normal cartilage lining is gradually worn away and the underlying bone is exposed resulting in pain and limited mobility of the affected joints. From the times of Hippocrates, OA or arthrosis deformans, it was believed that it is a chronic form of gout. It was only in 1782, when William Heberden coined the term *Digitorum nodi* and nowadays these small nodes are named after him. Heberden, noticed that these nodes had no connection with gout. The term OA as we use it today was coined by Garrod in 1890.

11.2 Epidemiology

As mentioned above, OA is the most common form of arthritis worldwide, one of the most common chronic health conditions, and a leading cause of pain and disability among adults. OA prevalence and incidence are different across studies, but it is generally accepted that both are high, especially after the age of 50. Females are affected more than males. Furthermore, lower socioeconomic status is related with increased risk of OA. Obesity is a well-recognised risk factor that leads to the development of OA. It is a key risk factor for knee OA, increasing the risk three-fold but also accelerating progression in established cases. Weight loss is associated with a lower prevalence of generalised OA. Traumatic joint injury is another major risk factor for OA, particularly at the knee and ankle.

11.3 Aetiopathogenesis

In OA the articular cartilage can no longer act as a shock absorber due to destruction of the extracellular matrix. Degradation of matrix components corresponds to failure of the cartilage to withstand cyclic loading, which, in turn, accelerates further degradation in the load-bearing regions. This is the mechanical-stress theory which involves low grade inflammatory processes as well. Thus, other joint tissues, such as the subchondral bone, the synovial capsule, and the membrane, are also involved in the disease process.

11.4 Signs and Symptoms

OA has a gradual onset. It may take several years before the damage to the joint becomes evident. In addition, only a third of those with radiographic findings compatible with degenerative arthritic changes report pain or other symptoms. Intermittent, mechanical pain of the affected joints may be the first symptom, which gradually becomes constant and more intense. Stiffness that tends to follow periods of inactivity, such as sleep or sitting usually lasts for less than 30 minutes and it is usually present in advanced stages. Swelling or tenderness in one or more affected joints can also be noticed. On clinical examination, hands, hips, knees and feet have typical findings.

- *Hands*: bony enlargement of the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints, called Heberden's and Bouchard's nodes respectively, and squaring of the carpometacarpal (CMC) joints are the most prominent findings of hand OA. Tenderness and partial loss of range of motion (ROM) may appear.
- *Knees*: bony enlargements (osteophytes) usually laterally to the joint line with swelling (occasionally) and limited ROM. Kellgren-Lawrence system for classification of knee OA is the most commonly used. Wasting of the quadriceps muscle is not uncommon. Crepitus on passive ROM is due to irregularity of the opposing cartilage surfaces. Joint malalignment can be seen in up to 50% of patients with advanced knee OA (genu varum mostly, but genu valgus may be present). Ligamentous structures may be affected (pseudolaxity of medial collateral and lateral collateral ligaments).
- *Hips*: patients always complain about groin pain when the hips are affected. ROM can be reduced, especially internal rotation and abduction.
- *Feet*: bony enlargement of the 1st MTP joint and hallux valgus deformity are the two most common findings in feet OA. Hallux rigidus can be present. Cervical and lumbar spine involvement is not uncommon.

11.5 Diagnostic Modalities

Diagnosis of OA can be made after a thorough clinical examination. Plain radiography may be the only diagnostic modality needed to assist with the definitive diagnosis.

Imaging: The radiographic hallmarks of OA are: normal mineralization, non-uniform loss of joint space, absence of erosions, subchondral new bone formation, osteophyte formation, cysts, subluxations, unilateral/bilateral asymmetrical distribution. Other imaging modalities used in OA are computed tomography (CT),

magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSUS). With the use of the above, the axial as well as the appendicular skeleton are visualised in detail.

Laboratory: there are no specific findings in primary OA. The acute phase reactants usually are within normal limits. Synovial fluid analysis shows a white blood cell count less than 2000 cells/mm³.

11.6 Management

The management of OA is somewhat more symptomatic. Education of the patient and prevention of the modifiable risk factors can lead to a better prognosis. Exercise improves ROM and muscle strength. Intra-articular corticosteroids and viscosupplementation seem to be beneficial in some patients. In advanced cases, mobility aids and braces can help in the everyday life, but surgical interventions (i.e. knee/hip arthroplasty) are needed as a definite solution, with generally good results.

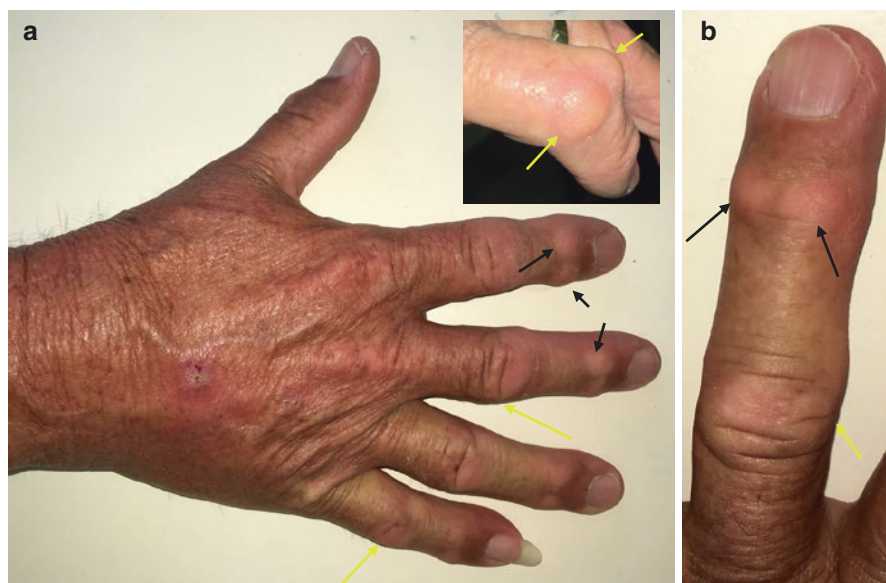
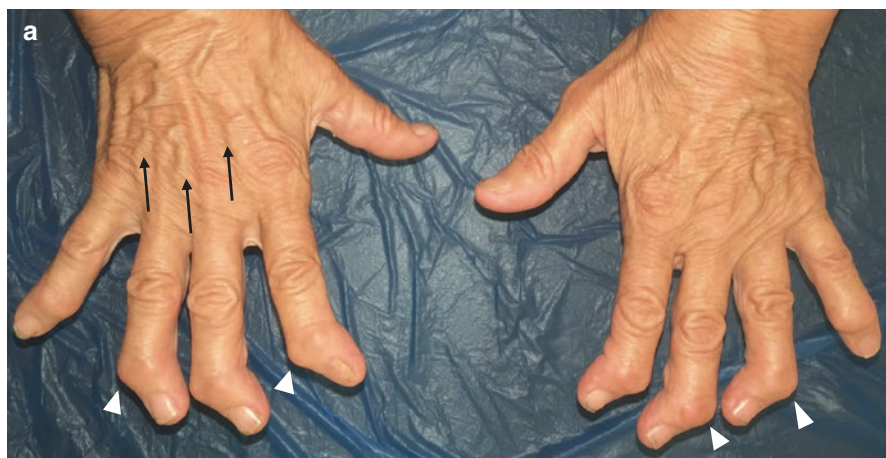
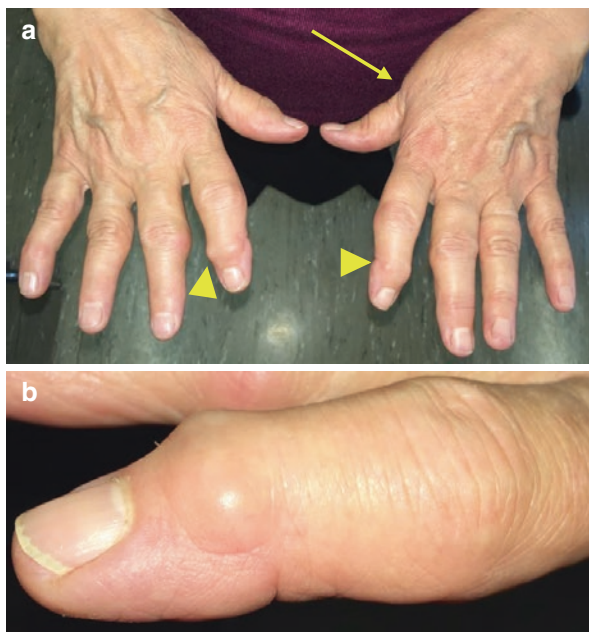


Fig. 11.1 Hand osteoarthritis

Typical hand findings due to OA. Heberden's and Bouchard's nodes are two common clinical findings when examining a patient suffering from OA. These nodes, are in fact, bony growths. Heberden's nodes are those found on the DIPs (black arrows, Fig. 11.1a, b), whereas Bouchard's nodes are those found on the PIPs (yellow arrows). Figure 11.1b shows the middle finger of the same patient with Heberden's nodes in detail while the insert figure shows Bouchard's nodes in detail.

Fig. 11.2 Nodal osteoarthritis

Nodal OA is a clinically distinct form of OA, with a strong genetic component. Characteristically affects the interphalangeal (IP) joints of the fingers with a predilection to DIPs over PIPs and the CMC joints of the thumbs. The onset is typically episodic and additive in pattern. The lesions can be associated with considerable deformity and subluxation (yellow arrowheads, Fig. 11.2a). Also, there is osteophyte formation and subluxation of the 1st CMC joints resulting in characteristic squaring of the hands (yellow arrow). In Fig. 11.2b, prominent Heberden's and Bouchard's nodes with mild subluxation of the PIP joint of the index finger.

**Fig. 11.3** Erosive osteoarthritis

Erosive OA is the name sometimes given to describe a rarer variant of nodal OA, which is characterised by instability and subluxation of the DIPs. There may be local inflammation followed by the development of more destructive subchondral erosions. In Fig. 11.3a, a 65-year old woman with severe OA affecting the distal interphalangeal joints is shown. Note also the Heberden nodes, subluxation of the DIP joints (white arrowheads) and interosseous muscle atrophy (black arrows). In Fig. 11.3b, Bouchard's nodes (yellow arrowheads) are more prominent, with similar findings of the patient in Fig. 11.3a.



Fig. 11.3 (continued)

Fig. 11.4 Knee osteoarthritis
Knees are also a common site affected by OA. On clinical examination crepitus is a common finding suggesting degenerative changes of the joint. Bony swelling, painful limitation of movement and deformity, Baker's cysts or other synovial cysts may occur. Figure 11.4a shows a moderately swollen knee whereas in Fig. 11.4b severe swelling is present on both knees. Skin incision sites after total knee arthroplasty (Fig. 11.4c, black arrowheads).

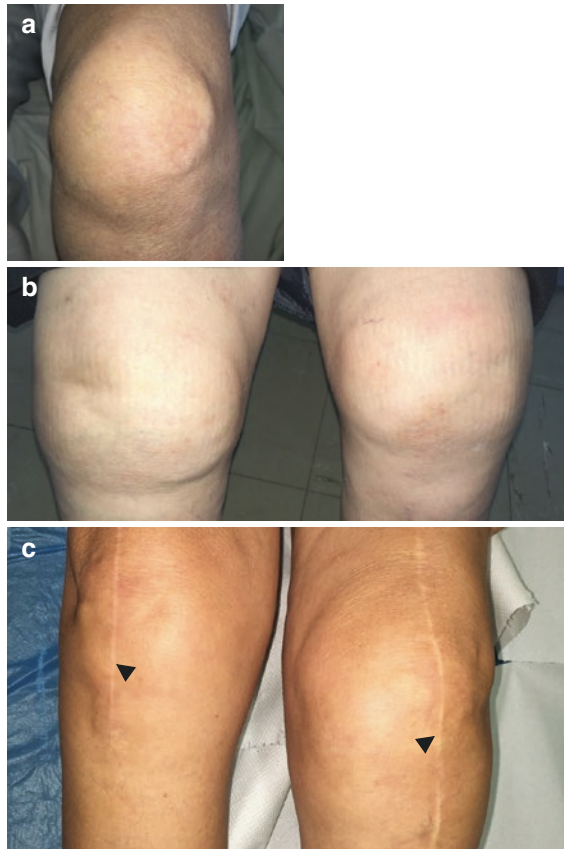


Fig. 11.5 Genu varum due to osteoarthritis

Figure shows a patient with medial compartment arthritis resulting in genu varum deformity. This is a typical presentation of patients with long-standing severe OA of the knees. The black dashed lines show the severe malalignment of both lower limbs. In most cases, these deformities can be corrected with knee arthroplasty.



Fig. 11.6 Hallux valgus deformity

Hallux valgus describes a forefoot condition in which the 1st metatarsal is medially deviated and the hallux is laterally deviated (black lines) creating a medial prominence at the 1st metatarsophalangeal (MTP) joint (bunion – black arrows). This condition, as it progresses becomes painful, especially with footwear. It commonly affects women and more than 80% of cases have a family history of hallux valgus. Along with the hereditary predisposition, a patient with splayfoot or use of improper shoes may cause a hallux valgus deformity. After the onset of OA, the impairment of joint mobility can proceed very quickly and it can be presented as hallux limitus (limited ROM of the 1st MTP) or hallux rigidus (no movement at all). Usually, the second toe crosses over the first, as seen on the left foot of the above figure.

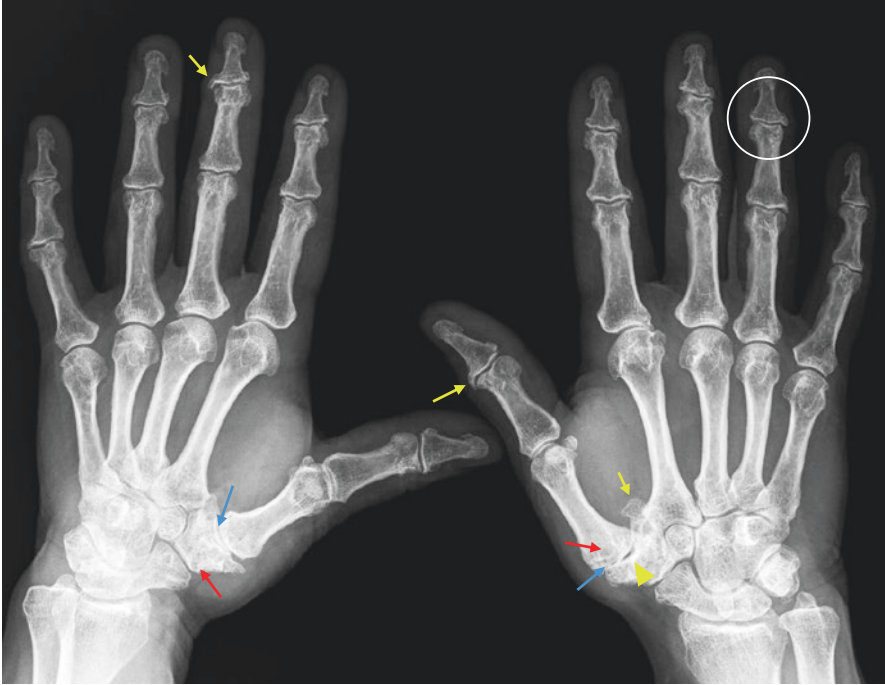


Fig. 11.7 Radiographic findings in osteoarthritis – hands

By the age of 65, eighty percent of people have some radiographic evidence of OA, although only one in four is symptomatic. OA is characterised by remodeling of the anatomy of the joint and proliferation of new bone in the form of osteophytes (yellow arrows), as well as by focal degeneration of articular cartilage. In addition, bone sclerosis, subchondral bone cyst formation, and asymmetric joint space narrowing are some other radiographic findings of the disease. The joints most frequently affected are the spine, hips, knees and the small joints of the hands and feet.

This patient has advanced OA. Note the complete loss of joint space in the 1st CMC joints bilaterally (blue arrows), subchondral cyst formation (red arrows), small osteophytes and erosions (yellow arrows), asymmetric joint-space narrowing with the “seagull” wing appearance caused by lateral osteophytes and central indentation (white circle), and bone sclerosis (yellow arrowhead).

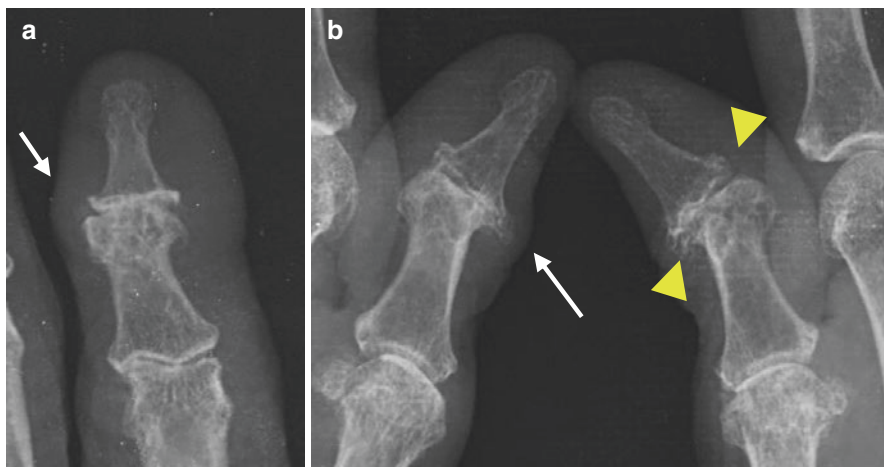


Fig. 11.8 Radiographic findings in erosive osteoarthritis – hands
Erosions of the DIP joints (Fig. 11.8a, b) with subluxation (Fig. 11.8b, yellow arrowheads). Note also the soft tissue contour (white arrows – Heberden's nodes).

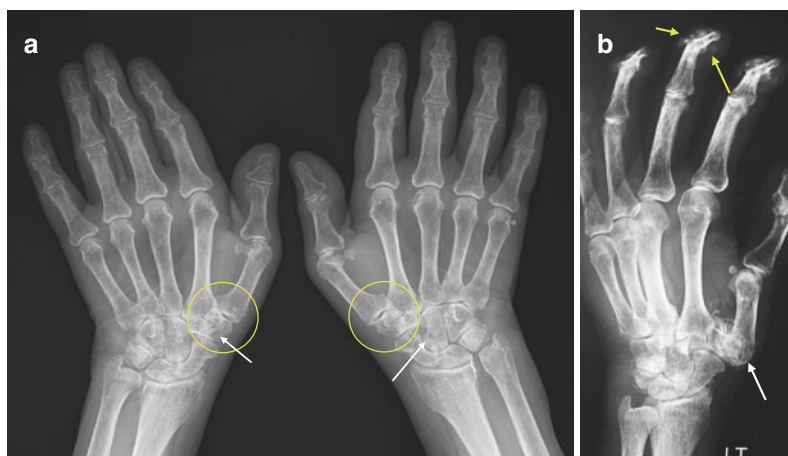


Fig. 11.9 Hand osteoarthritis – involvement of the 1st carpometacarpal joint

Osteoarthritic changes of the 1st CMC joint is very common, especially after the age of 50. Thumb CMC OA leads to pain, laxity and weakness of the joint. The Eaton-Littler classification describes four stages of OA changes and it has been proposed as a guide to surgical intervention. For correct results, a true lateral radiograph of the trapeziometacarpal joint of the thumb with the sesamoid bones superimposed on one another must be ordered. Nevertheless, a simple posteroanterior view can show OA changes of the 1st CMC as well.

Stage I: subtle carpometacarpal joint space widening. Stage II: joint narrowing due to cartilage wear and osteophytes <2 mm. Stage III: joint narrowing and osteophytes >2 mm. Stage IV: trapezioscapoid involvement with major trapeziometacarpal narrowing.

In Fig. 11.9a and b, the main findings are: involvement of the 1st CMC (yellow circles), bone cysts in the carpal bones (white arrows), PIP and DIP involvement. In Fig. 11.9b note also the presence of calcifications (yellow arrows).

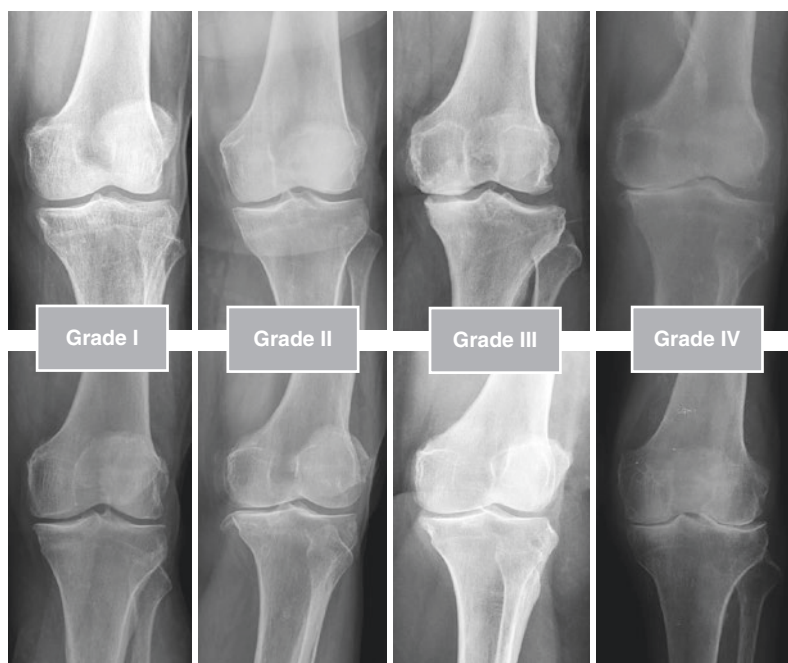


Fig. 11.10 Osteoarthritis grading system (Kellgren – Lawrence grading)

There are a number of grading systems in knee OA, but the Kellgren – Lawrence grading system is the most widely used and accepted standard for diagnosis of knee OA. Even if a clinician uses this system, it has to be clear that not all patients will have exactly the same radiographic appearance.

Grade I: doubtful narrowing of joint space and possible osteophytic lipping.

Grade II: definite osteophytes, definite narrowing of joint space.

Grade III: moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour.

Grade IV: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

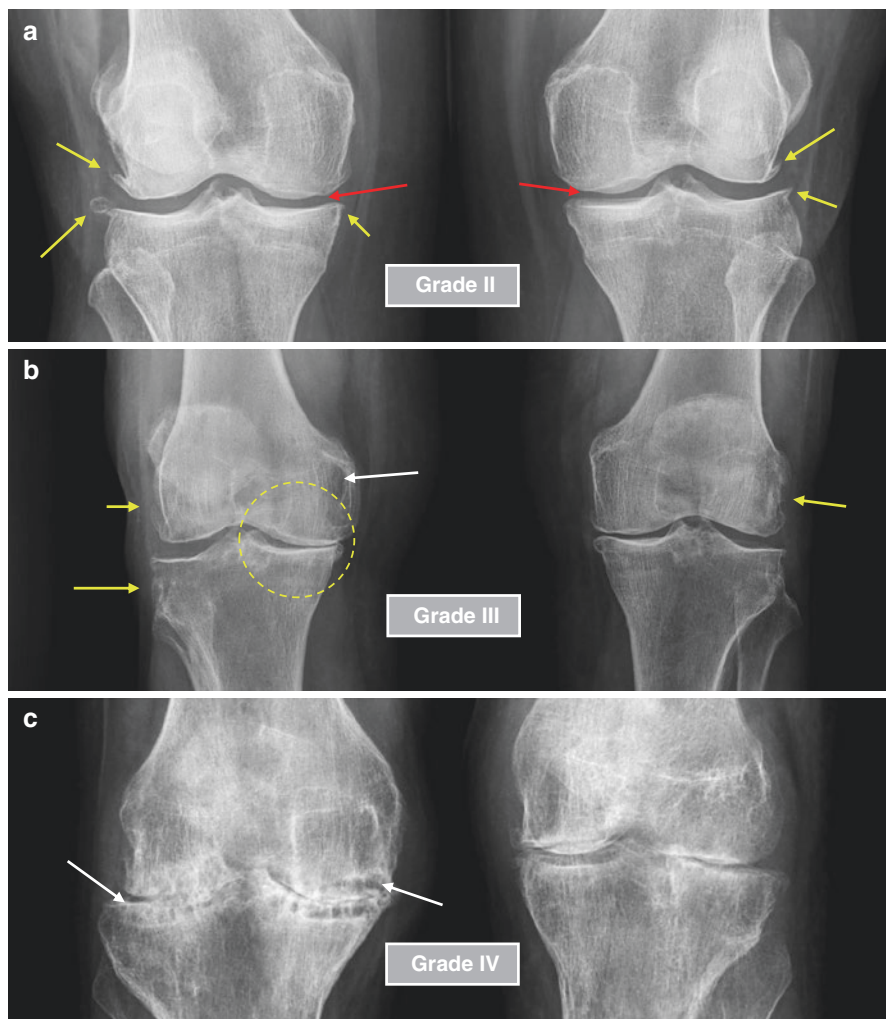


Fig. 11.11 Knee osteoarthritis in detail

As mentioned in Fig. 11.10, not all patients will have exactly the same radiographic findings. In Fig. 11.11a, there are definite osteophytes (more prominent on the lateral side of the joint – yellow arrows) and definite narrowing of the joint space (medially > laterally – red arrows). Figure 11.11b shows also sclerosis (medially > laterally – yellow circle) and deformity of the bone contour (laterally – yellow arrows). In the middle femoral condyle there is also a cyst (geoda – white arrow). Figure 11.11c depicts a totally destroyed joint with marked sclerosis, no joint space and multiple subchondral cysts (right knee – white arrows), while on the left knee note the definite space narrowing in both sides.

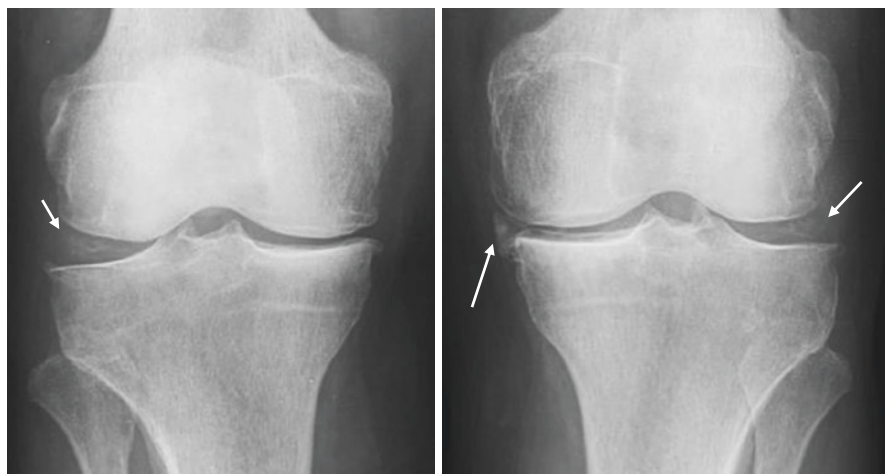


Fig. 11.12 Knee osteoarthritis with chondrocalcinosis

OA can coexist with calcium pyrophosphate dihydrate disease (CPPD). The diagnosis can be made by a plain radiographic assessment of the joint. Chondrocalcinosis is present (white arrows) with medial joint space narrowing, mild sclerosis and small osteophytes, in a patient suffering from knee OA.

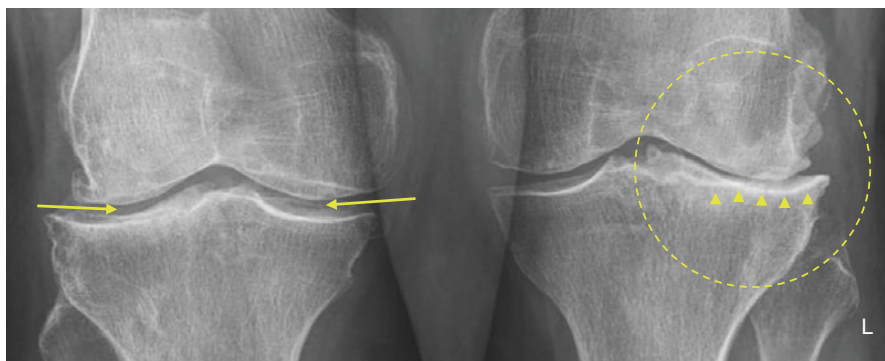


Fig. 11.13 Lateral compartment knee osteoarthritis

Usually, the medial compartment of the knee is affected (e.g. Fig. 11.12) but, the lateral compartment can be affected too (yellow dashed circle). Marked sclerosis is also evident (yellow arrowheads). When one of these compartments is affected, then it is called unicompartmental arthritis (left knee) but it is also possible to have both medial and lateral compartmental arthritis at the same time (right knee – equal space narrowing medially and laterally, yellow arrows).

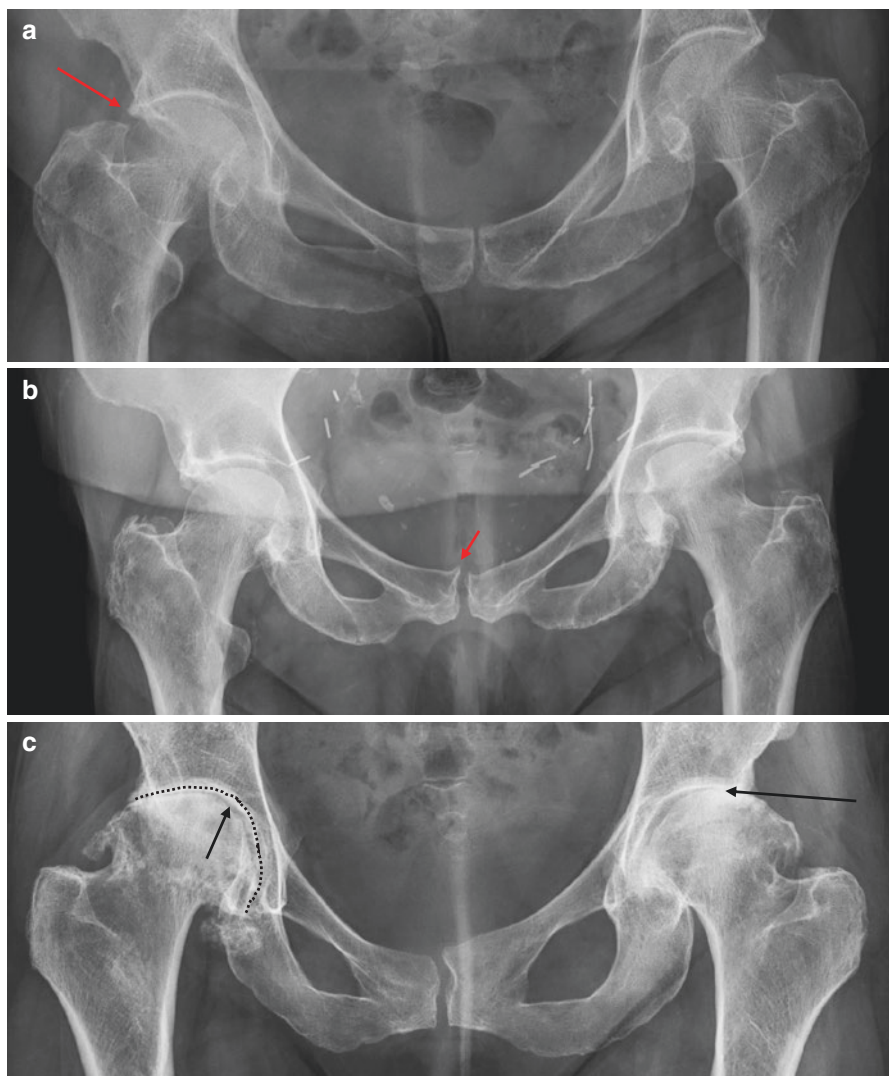


Fig. 11.14 Hip osteoarthritis

Hip OA is not an uncommon cause of pain, limited ROM and low quality of life in patients >65 years old. These three plain radiographs show hip OA of different stages (14a < 14c) with predominant superolateral joint space narrowing (black arrows), subchondral sclerosis of the bone adjacent to the joint space (black dashed line), and some marginal osteophytes (red arrow). In Fig. 11.14b an osteophyte of the symphysis pubis is evident. Symphysis pubis degeneration can cause severe groin pain in advanced stages.

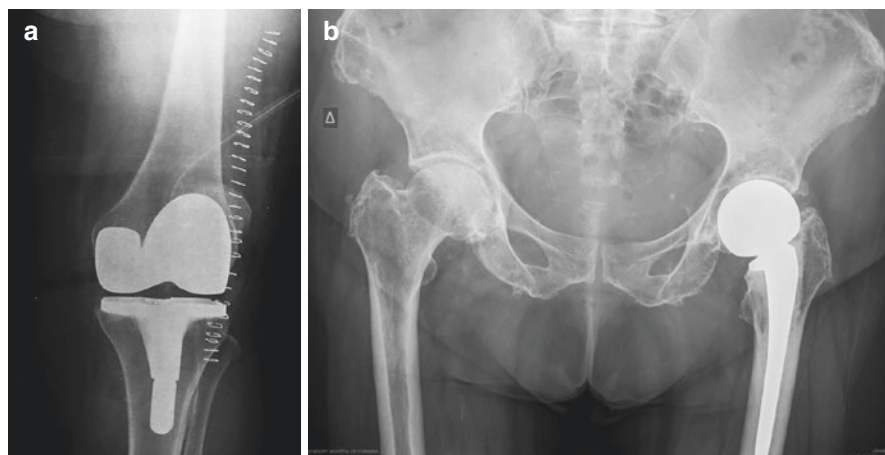


Fig. 11.15 Total joint replacement

Patients with knee OA who do not enjoy any alleviation of pain after trying non-pharmacologic and pharmacologic approaches should be considered for joint replacement surgery. Nowadays, total hip replacement (THR) and total knee replacement (TKR) are two common procedures in “end-stage” OA patients. Both, are cost-effective interventions and relatively safe. Patients’ quality of life improves significantly after a successful replacement. Infection after joint arthroplasty is a major concern and is often difficult to eradicate.

Clinicians should always bear in mind that the radiographic appearance of the joint should not be the sole criterion for arthroplasty but to those with significant symptoms and functional limitations.

Figure 11.15a and b show a TKR and a THR respectively due to severe OA. In Fig. 11.15b note also osteoarthritic radiographic changes affecting the right hip, as well as the great trochanter.

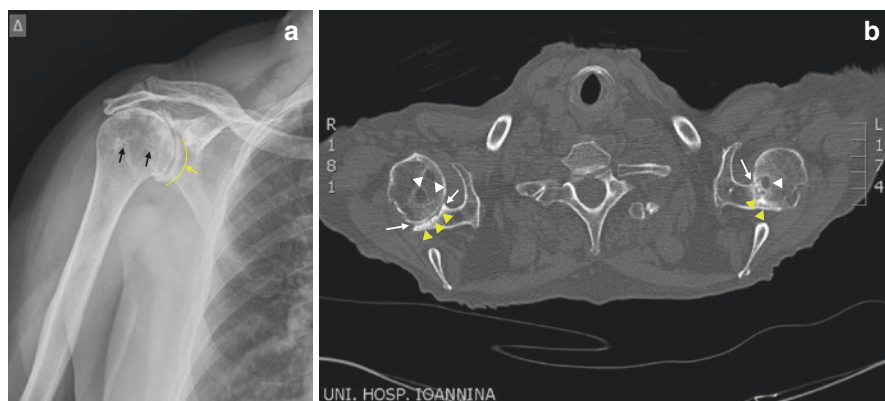


Fig. 11.16 Osteoarthritis of the shoulder

Figure 11.16a shows a patient with degenerative changes of the right shoulder. Bone cysts in the humeral head (black arrows), narrowing of the glenohumeral joint and marked sclerosis in the margins of the glenoid cavity (yellow arrow).

Figure 11.16b shows a patient with severe OA of both shoulders. There is marked joint space narrowing of the glenohumeral joints (left>right, white arrows), bone sclerosis (yellow arrowheads) and multiple bone cysts (white arrowheads).

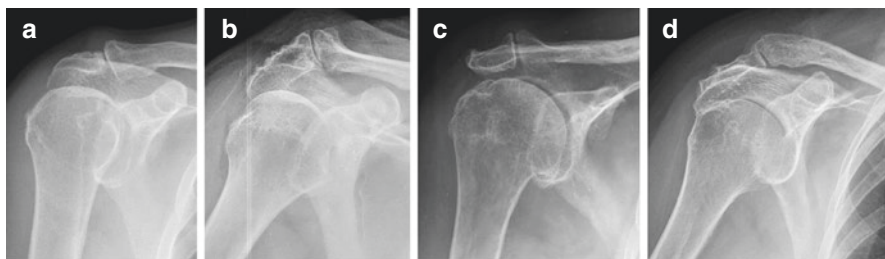


Fig. 11.17 Shoulder (shoulder osteoarthritis or degenerative arthritis of the shoulder)

The shoulder is made up of two joints, the acromioclavicular joint and the glenohumeral joint. OA is more commonly found in the acromioclavicular joint. Symptoms may include mild to excruciating pain when moving the shoulder or even at rest (sleeping) and as a consequence limited ROM. Figure 11.17a–d show different patients with degenerative changes of the acromioclavicular joint and narrowing of the glenohumeral joint space. When non-pharmacological and pharmacological approaches fail, then surgical treatments may help (e.g. total shoulder arthroplasty, hemiarthroplasty, resection arthroplasty).

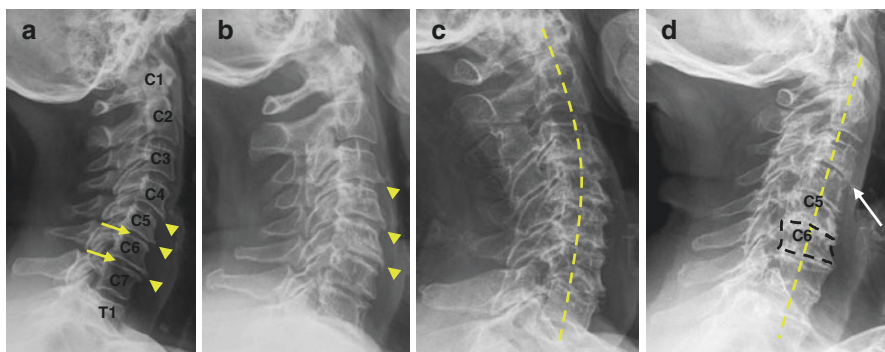


Fig. 11.18 Cervical spine (cervical spondylosis or cervical osteoarthritis)

Variable degenerative findings on plain x-rays of patients with OA. Cervical osteophytes and disc space narrowing are the main findings in OA. The osteophytes are beak-like and sometimes they can be fused. They must be distinguished from the bony syndesmophytes of ankylosing spondylitis (AS). These changes are caused by the normal wear-and-tear of aging. Common symptoms are neck stiffness and pain, headache, dizziness (when extending the neck) and shooting pain in the shoulders or arms.

Figure 11.18a) beak-like osteophytes C4-C6 (yellow arrowheads), disc space narrowing C5-C6, C6-C7 (yellow arrows).

Figure 11.18b, c more severe cases, with more degenerative changes in C2-C7.

Figure 11.18d severe degenerative findings. The cervical curvature has disappeared (yellow dashed line, compare it with the line from Fig. 11.18c). C5-C6 with no disc space. C3-C4 syndesmophyte (white arrow). Severe cervical spine body contour changes (black dashed rectangle – Fig. 11.18d).

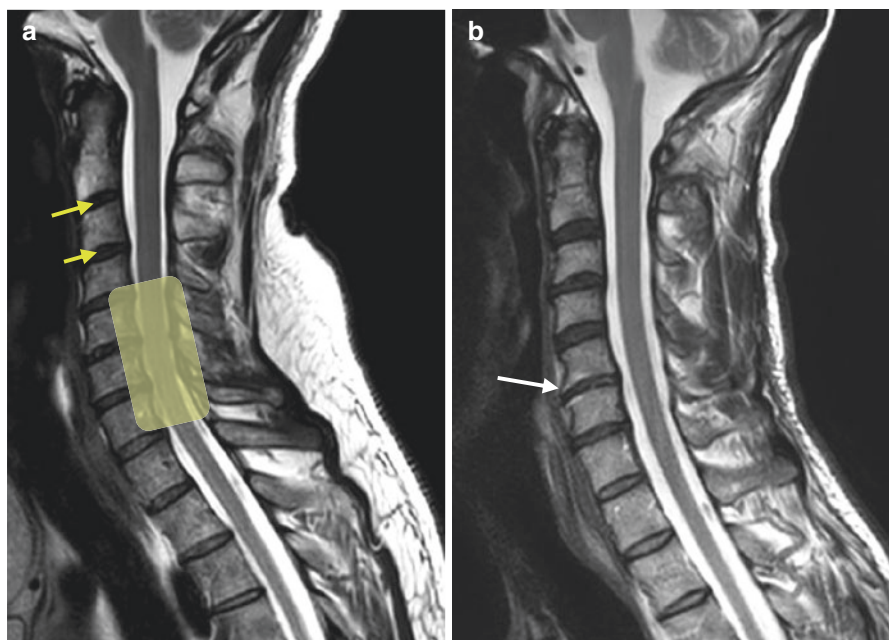


Fig. 11.19 MRI of the cervical spine in osteoarthritis

Figure 11.19a T2-weighted image in sagittal plane, disc protrusion and dehydration (yellow arrows) that result in a decrease of the anterior subarachnoid space at C4-C7 level (yellow faded rectangle)

Figure 11.19b T2-weighted image in sagittal plane, disc dehydration, disc space narrowing in C5-C6 with anterior osteophytes (white arrows).

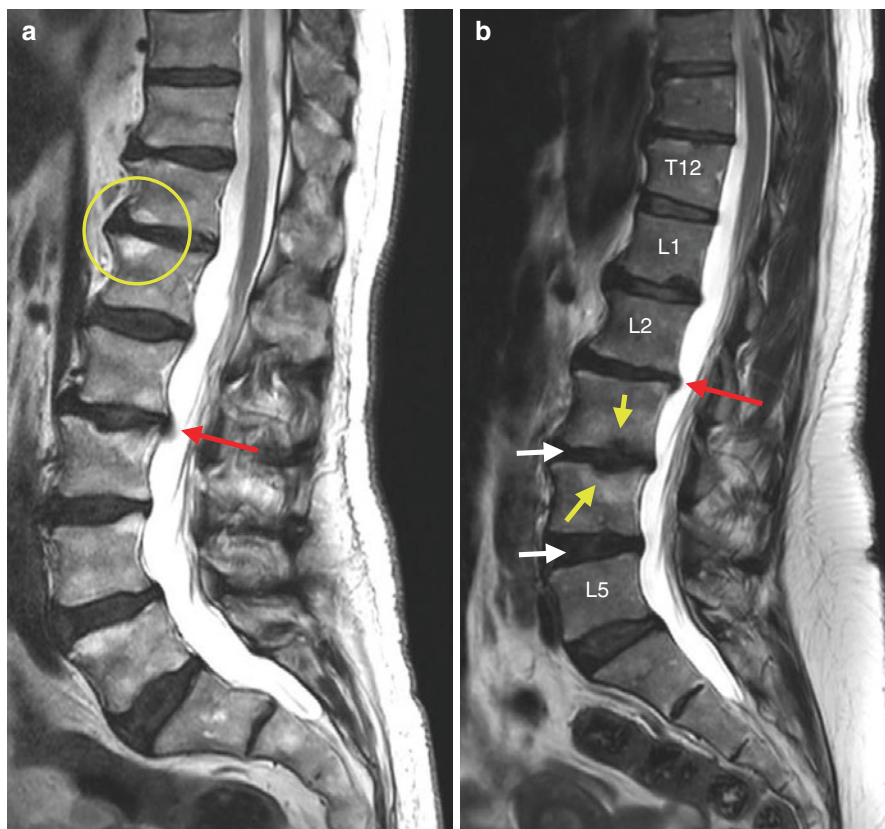


Fig. 11.20 MRI of the lumbar spine in osteoarthritis.

Figure 11.20a T2-weighted image in sagittal plane, disc protrusion (red arrows) and dehydration with the presence of osteophytes and degenerative changes of the epiphyseal plates (Modic I – yellow circle).

Figure 11.20b T2-weighted image in sagittal plane, osteophytes, disc protrusion and dehydration (white arrows). Schmorl nodes of the L3-L4 vertebrae (yellow arrows).

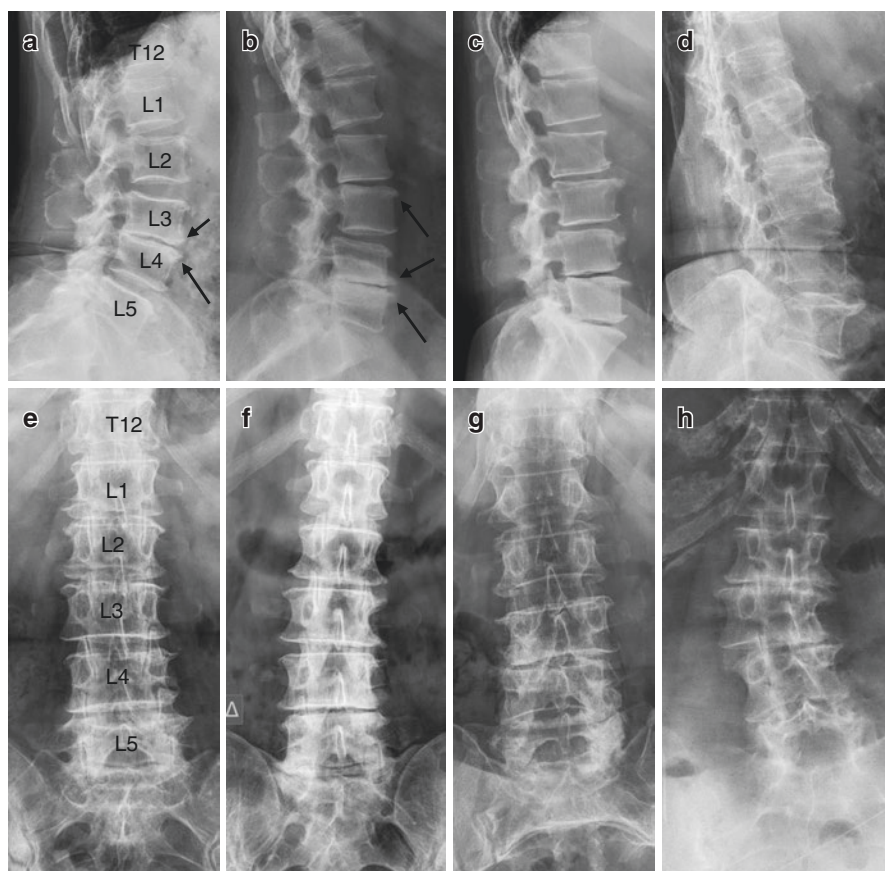


Fig. 11.21 Lumbar spine osteoarthritis.

Radiographic lumbar spine OA is very common, with estimates of prevalence ranging from 40–85%. Osteophyte formation and disc space narrowing (as described in Fig. 11.18) are the main radiographic findings in lumbar spine OA. A vertebral osteophyte is a bony outgrowth that arises from the periosteum at the junction of bone and cartilage and it has been shown to be a general indicator of age. Low back pain is the herald symptom which can lead to poor everyday quality of life. Utilisation of health care services resulting from low back pain is high.

In Fig. 11.21a–d and e–h there are lumbar spine radiographs of different patients with OA in lateral and postero-anterior view respectively. Note that most osteophytes arise at the sites where disc degeneration occurs. For example, in Fig. 11.21a, L3–L4 disc narrowing results in osteophyte formation as it is also shown in Fig. 11.21b L2–L3 and L4–L5 (black arrows). The same pattern appears in the rest of the radiographs as well.

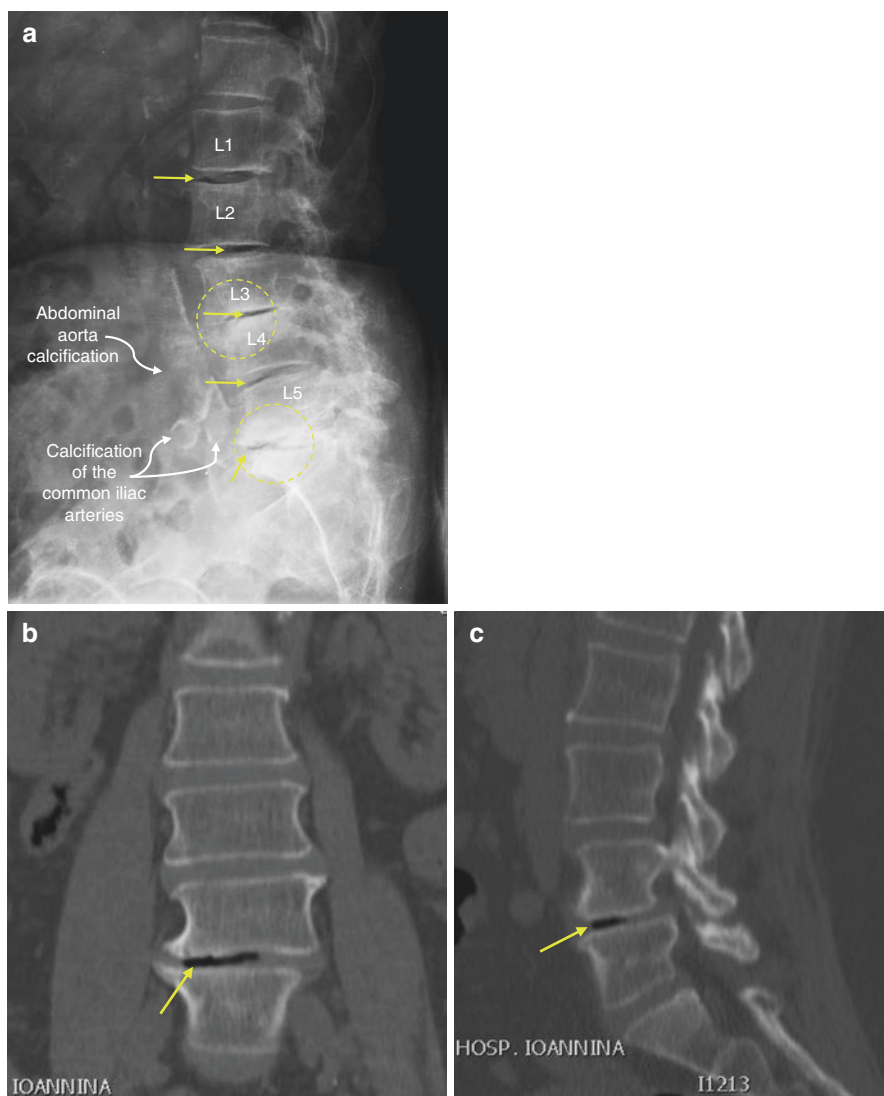


Fig. 11.22 Lumbar spine osteoarthritis and vacuum sign

In this lumbar spine lateral radiograph, severe OA changes are shown at L3-L4, L4-L5, and L5-S1 levels. There is osteophyte formation and disc space narrowing with spondylodiscitis involving L3-L4 and L5-S1 vertebral bodies (dashed yellow circles) with subchondral sclerosis. Note also calcification of the abdominal aorta with the common iliac arteries (Fig. 11.22a).

Vacuum sign is a radiolucent defect and it is caused by the presence of nitrogen gas accumulations in annular and nuclear degenerative fissure. Typically, it is found in the centre of the intervertebral discs and it is called central vacuum phenomenon/sign. In Fig. 11.22a, all the intervertebral discs from L1 to S1 present this sign (yellow arrows). Another patient with OA presenting the vacuum sign on CT of the lumbar spine (L4-L5, Fig. 11.22b).



Fig. 11.23 Sinus tarsi syndrome

The sinus tarsi (black asterisk) is an important space on the lateral foot, and contains important stabilising ligaments of the subtalar joint, fat tissue, nerve endings of the peroneal nerve and blood vessels. Symptoms may include persistent pain at the lateral ankle and a feeling of instability at the ankle. Usually, a previous traumatic ankle injury is the cause. Post-traumatic arthritis or osteoarthritic degenerative changes may occur if no treatment applied. This patient was complaining of deep ankle pain especially when walking. As you note, the sinus tarsi space is diminished and degenerative changes of the subtalar joint are evident (white arrow).

Fig. 11.24 Osteoarthritis of the foot

OA changes of the foot are as common as those presented in hand OA. The x-rays must be done with the patient in standing position, if it is possible. This x-ray reveals osteoarthritic changes in the 1st MTP joint bilaterally as well as both DIPs. Joint space narrowing (black arrow) and small osteophytes (white arrows) can be seen. Diffuse osteopenia is also present with some degenerative changes of the midfoot.



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Chapter 12

Crystal Arthropathies



12.1 Introduction

Crystal arthropathies are a group of joint disorders due to deposition of crystals in and around joints which lead to joint destruction and soft tissue disturbances (swelling, redness, masses etc.). Clinical presentations of the different types of crystal arthropathies are often characteristic enough to differentiate them from each other, but mistakes can be made, leading to delayed or incorrect management. Gout is the most common form of crystal arthropathies. First identified by the Egyptians in 2640 BC and later by Hippocrates in the 5th century BC, who referred to as “the unwalkable disease”. Throughout history, gout has been associated with rich foods and excessive alcohol consumption and has been referred to as the “disease of kings”. Calcium pyrophosphate dihydrate disease (CPPD/pseudogout) and basic calcium phosphate (BCP/hydroxyapatite) are the two other forms of crystal arthropathies.

12.2 Epidemiology

Gout is the most common form of inflammatory arthritis. The reported prevalence of gout worldwide ranges from 0.1% to approximately 10%, and the incidence from 0.3 to 6 cases per 1000 person-years. Both prevalence and incidence is highly variable across various regions of the world. Developed countries show a higher prevalence than developing countries. Major risk factors for gout include hyperuricaemia, genetics, dietary factors, medications, comorbidities and exposure to lead.

Pseudogout needs the identification of CPPD crystals in joint fluid or articular tissue in order to make a diagnosis. Because joint aspiration or biopsy is impractical in population studies, presence of radiographic chondrocalcinosis often has been used in epidemiologic and clinical investigations to study CPPD disease. The prevalence of radiographic chondrocalcinosis in the knee joints varies from less than 4% in those under age 70–27% in those over 85. Mean age at presentation is between sixth and seventh decades of life. Female to male ratio is 2–3:1. Most studies agree that the prevalence of radiographic chondrocalcinosis increases with age.

BCP deposition is usually asymptomatic but can potentially lead to destructive arthropathy. The epidemiology of BCP crystal deposition is poorly understood. Although periarticular BCP crystal deposits occurs at all ages and in both sexes, intra-articular BCP crystal deposition tends to associate with increasing age and OA.

12.3 Aetiopathogenesis

Gout is the result of the pathogenic effect of monosodium urate (MSU) crystals in the joints and soft tissue. Uric acid comes from the metabolism of purine nucleotides. Purine metabolism leads to inosine then hypoxanthine. Hypoxanthine is metabolised to xanthine, which is metabolised to uric acid. The enzyme xanthine oxidase catalyzes the last two steps and is the major site for pharmacologic

intervention by allopurinol. If the body is unable to metabolise urate, hyperuricaemia develops. As urate levels increase, crystals develop and precipitate into the joint leading to arthritis. Urate crystals activate monocytes and macrophages which try to clear the crystals by phagocytosis. This leads to the release of proinflammatory cytokines and chemokines triggering a cascade of acute inflammatory reaction. An additional proposed mechanism involves the role of an inflammasome and interleukin (IL)-1 in the pathogenesis of inflammation induced by MSU and CPPD. Pathogenesis of BCP is complex. It can be secondary to intracellular calcium increase, leading to the activation of calcium-dependent pathways.

12.4 Classification Criteria

The 2015 American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) classification criteria for gout are the latest ones. The entry criterion is at least one episode of swelling, pain, or tenderness in a peripheral joint or bursa. Presence of MSU crystals in a symptomatic joint or bursa or tophus is a sufficient criterion. There are also clinical, laboratory and imaging criteria. The entry criterion must be met. If sufficient criterion is met, patient is classified as having gout without applying other criteria. If not, a score ≥ 8 is required to classify as gout. If serum urate < 4 mg/dL a score of -4 points is applied; if serum urate ≥ 4 – 6 mg/dL the score is 0 points; if ≥ 6 – 8 mg/dL the score is 2; if ≥ 8 – 10 mg/dL the score is 3; if > 10 mg/dL then the score is 4. If polarizing microscopy of synovial fluid from a symptomatic joint or bursa by a trained examiner fails to show MSU crystals, then -2 points. If synovial fluid was not assessed, the score is 0. If imaging evidence of urate deposition in symptomatic joint or bursa or gout-related joint damage, the score is 4; if absent or not done, the score is 0.

12.5 Signs and Symptoms

Gout is clinically manifested as acute inflammation of the involved joint or soft tissue. In general, gout includes joint swelling in both the lower and upper extremities with a predilection to the first metatarsophalangeal (MTP) joint (podagra). Any peripheral joint can be involved (feet, ankles, knees, hands, wrists, elbows). Acute gout can also occur in the bursae, such as the olecranon or prepatellar bursae, where it causes bursitis. Tendons, such as the Achilles tendon can also be involved. Systemic manifestations such as fever and malaise may develop. The arthritis in acute gout usually manifests as asymmetric monoarticular or oligoarticular inflammation. Without treatment it may last for 3–10 days, and resolves spontaneously, but when the attacks occur more frequently, they tend to last longer and do not resolve completely leading to chronic gouty arthropathy. Chronic arthropathy eventually leads to erosions and joint destruction.

CPPD encompasses a variety of clinical manifestations. It may be asymptomatic, but it may mimic gout (pseudogout), rheumatoid arthritis (RA) (pseudo-rheumatoid

arthritis), and OA (pseudo-OA). The knee is the most commonly affected joint, followed by the wrist. Acute podagra involving the 1st MTP joint is rare. In contrast to the brief attacks of acute gouty arthritis that last only some days, acute attacks of CPPD disease may last for weeks to months. It is important to remember that CPPD disease can be a presenting sign of hyperparathyroidism, hypophosphatasemia or other metabolic disorders. Thus, an appropriate screening is indicated, especially in patients younger than 60 years of age who present with CPPD symptoms. Similar to gout, CPPD disease can manifest with systemic features such as fever and malaise, especially in the elderly. The acute attacks can involve one or multiple joints.

BCP crystals are mainly responsible for acute peri-arthritis that involves all possible tendon or capsular sites. The most affected site is the shoulder. The formed calcifications can be unfragmented and dense, with a round shape, at the asymptomatic phase. When they start to be fragmented the inflammation starts provoking pain and even limited range of motion (ROM) of the affected joint.

12.6 Diagnostic Modalities

Synovial fluid analysis is considered the technical standard for evaluating patients with gout or acute CPPD arthritis not only as a diagnostic procedure but also to rule out septic arthritis. The collected fluid needs to be processed by Gram stain, culture, and microscopic examination. The white blood cell count is useful to estimate the degree of inflammation. Under polarized light, MSU crystals are strongly negative birefringent and have a needle-shape, whereas CPPD crystals are weakly birefringent and have a rhomboid shape. BCP crystals are not detectable by light polarized microscopy. Alizarin red staining can provide information on BCP crystals.

Laboratory tests such as serum urate levels, acute phase reactants, serum creatinine, full blood count (FBC) and liver function tests (LFTs) are useful for evaluating other comorbid diseases or to monitor and adjust the dose of urate-lowering therapy. Of note, serum urate levels are not helpful indicators during acute gouty attacks because they can fluctuate from low to high. Measuring a 24 h collection of urine urate is a very useful test to identify patients who overproduce urate. BCP disease may present with no laboratory abnormalities.

Imaging studies: a high-end musculoskeletal ultrasound (MSUS) equipment can detect crystal depositions before they can be seen on plain x-rays. MSUS is a not invasive, safe, easily accessible and a well-accepted imaging technique by the patient. In gout, MSUS can be useful for the diagnosis and management from the initial manifestations of the disease in comparison with other imaging modalities. Specific signs in gout are the double contour sign, aggregates and tophi. The double contour sign is defined as an abnormal hyperechoic band over the superficial margin of the hyaline cartilage (HC). As non-specific findings, inflammatory abnormalities (joint effusion and synovial hypertrophy) and structural lesions (such as bone erosions) can be detected.

Gout – radiographic findings: Urate crystal deposits in tissues with poor blood supply such as cartilage, tendon, sheaths, bursae etc. Acute attacks occur at the night

when the blood supply of the body is decreased and the body temperature is low. Both these factors facilitate urate crystal precipitation. Only 45% of patients with gout manifest radiographic bone changes and then only 6–8 years after the first attack. The radiographic changes indicate the chronicity of the disease process.

Gouty arthritis has several characteristic radiographic features. Erosions, which are usually sharply margined, are initially periarticular in location and are later seen to extend into the joint. An overhanging edge of erosion is a frequent identifying feature. Usually, there is a striking lack of osteoporosis, a feature helpful in differentiating this condition from RA. The reason of this is that acute gouty attack is short in duration to allow the development of the periarticular osteoporosis so often seen in RA patients. Other radiographic features of chronicity in gout attack is punched-out erosions with sclerotic borders. Chronic tophaceous arthritis is created by the deposition of urate crystals in soft tissues. Tophi are dense tissue masses usually found in the periarticular area along the extensor surface of the bone. Urate crystals are not radio-opaque. However, calcium may precipitate with the urate crystals to varying degrees, creating variation in the density of tophi.

CPPD has characteristic findings on plain x-rays. Conventional radiographs provide important evidence for the diagnosis of CPPD disease and may assist to differentiate CPPD from other types of arthritis. Although chondrocalcinosis is the radiographic finding that is most closely aligned with CPPD disease, other radiographic findings may assist to differentiate primary OA from CPPD. These include: hook-like osteophytes involving the metacarpophalangeal (MCP) joints, annulus fibrosus calcification, disc degeneration with vacuum phenomenon and subchondral erosions, and vacuum phenomenon of the sacroiliac joints as far as it concerns the axial skeleton. Other radiographic features include radio-carpal or patello-femoral narrowing of the joint space with cysts formation and subchondral collapse. Chondrocalcinosis is seen in the knees, the wrists, and other joints such as intervertebral discs and symphysis pubis.

Hydroxyapatite deposition disease: the radiographic findings are the following: Periarticular calcification (a. early deposition in linear and poorly defined, often blending with the soft tissue, b. with time the calcifications become denser, homogeneous, well-delineated and circular).

Soft tissue swelling, with occasional reactive sclerosis. Single-joint distribution. Occasionally multiple joints. Distribution in shoulders, hip, wrists, elbow, and neck in decreasing order of frequency. Finally, in crystal arthropathies, other imaging modalities are used when indicated such as computed tomography (CT) and magnetic resonance imaging (MRI).

12.7 Management

The main concern in the acute attacks of crystal arthropathies is to reduce inflammation and pain, and also to prevent future joint erosions and flares. Treatment depends on the clinical presentation and findings. Non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids (CS), interleukin (IL)-1 inhibitors and urate-lowering drugs can be used depending on the clinical presentation.



Fig. 12.1 Gout – acute arthritis

Acute arthritis in gout, typically affects the first MTP and it is called podagra. Figure 12.1a depicts a patient with gout. It was the first attack, with mild to moderate erythema of the 1st MTP, mild oedema and tenderness on palpation. Figure 12.1b, shows a patient with recurrent attacks. There is a dusky, shiny erythema overlying swollen 1st MTP joint. This patient was unable to weight bear due to excruciating pain even in mild movements of his foot. He was a heavy drinker and was not taking any medicines for gout prophylaxis. In Fig. 12.1c and d another example of an acute episode of gout is shown with the corresponding plain radiograph. Note the bone erosions and cyst formation affecting the 1st and 5th MTP joints (white arrows) and the swelling of the soft tissue around the 1st MTP joint (white arrowheads). Occasionally, ankle, other toes, knees or fingers (Fig. 12.1e) are affected (black arrowheads).



Fig. 12.2 Chronic tophaceous gout

Tophaceous gout is a chronic form of gout. For reasons that remain unclear, not all gouty patients present with acute arthritis as the first sign. In Fig. 12.2a–c, tophi have been developed on the fingers of those patients (white arrows). Tophi, are usually painless, hard deposits of uric acid that can appear virtually at any joint. Tophaceous deposits can be distinguished from calcinosis by their radiological appearance. Calcinotic deposits are more radio-opaque than tophaceous and are often described as giving a “halo” effect (see below – Fig. 12.5a). Other, less common affected sites are the elbows. In Fig. 12.2d and e, there is a patient with chronic gouty olecranon bursitis bilaterally. Gout may be presented for the first time as an acute olecranon bursitis. In order to set a correct diagnosis, the clinician should aspirate a sample for analysis. MSU crystals ingested by polymorphonuclear leucocytes under the microscope, will confirm the diagnosis. Renal function test should always be investigated in such patients.

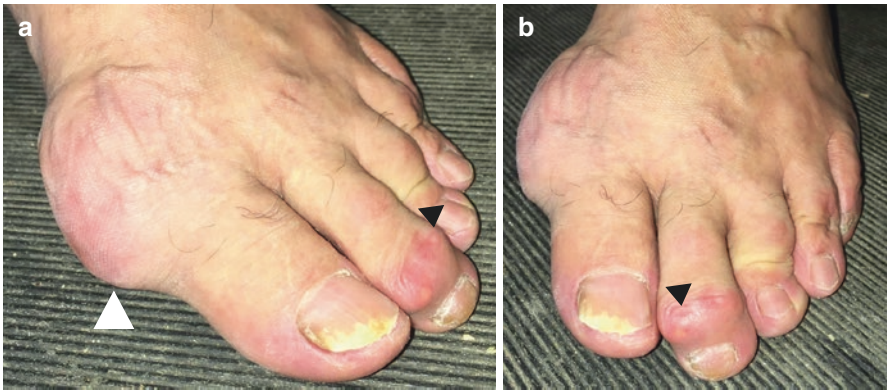


Fig. 12.3 Acute and chronic features of gout
A patient with chronic manifestations of gout should be on lifelong treatment for the prevention of recurrences. This patient has a large tophus on the 1st MTP (white arrowhead) as well as two smaller on the distal interphalangeal joint (DIP) of the second toe of the foot (black arrowheads). He discontinued the treatment on his own and developed de novo an acute gout flare of the 1st MTP.



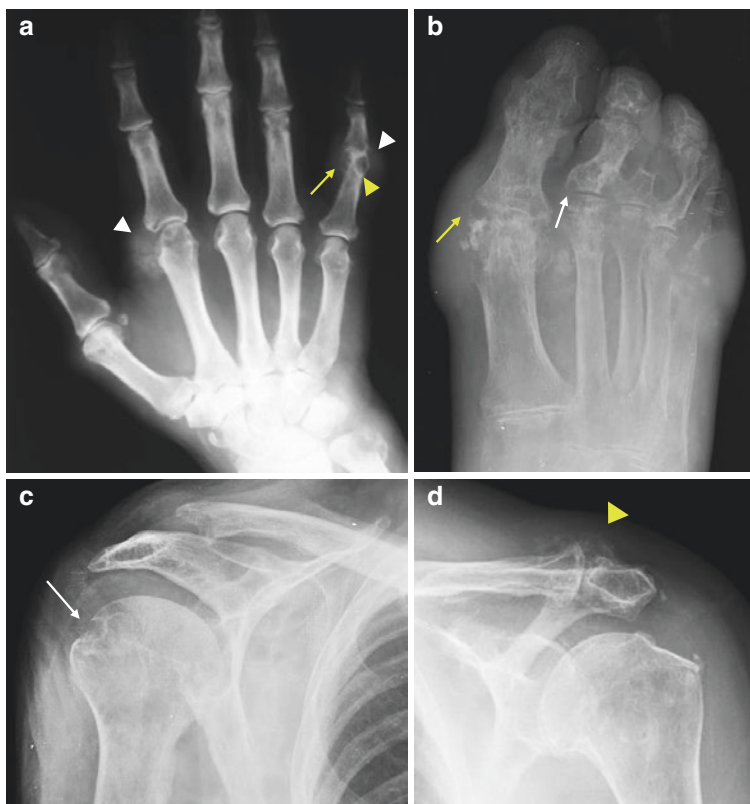


Fig. 12.5 Radiographic findings in gout

In the acute setting of the first gout arthritis there may not be present any radiographic findings. Erosions may appear after years, usually 6-8 years after the initial attack. The feet and hands are commonly affected in an asymmetric pattern. Tophaceous deposits can be distinguished from calcinosis by their radiological appearance (Fig. 12.5a–d). They are less radio-opaque than calcinotic deposits and are often described as giving a “halo” effect (white arrowheads – Fig. 12.5a). Punched-out erosions (or mouse bitten) are very typical for patients with gout (white arrows – Fig. 12.5b, c). As the erosion develops, the edges of the cortex can be remodeled in an outward fashion, creating an overhanging edge (yellow arrows – Fig. 12.5a, b). Intra-osseous lesions are another finding consisting of intra-osseous tophus with or without calcification that tend to expand (yellow arrowhead). In contrast to RA, there is no periarticular osteopenia. Of note is that such erosions are rare findings in the shoulders. Figure 12.5d shows tophaceous deposits in the acromioclavicular joint (yellow arrowhead).

Fig. 12.4 Severe cases of tophaceous gout

In the above figures, patients are suffering from longstanding tophaceous gout. Nodular masses of uric acid crystals (tophi) are deposited in various soft tissue areas of the body. Large tophi can easily be seen in Fig. 12.4a–d, which can lead to disastrous effects of the affected joints. In Fig. 12.4d some tophi have been ulcerated. Figure 12.4e shows a patient with an ulcerating tophus associated with chronic gouty arthritis of the DIP joint of the middle finger. Patients with tophaceous gout rarely develop ulcers, but when they do occur, these ulcers are difficult to treat. IL-1 inhibitors are used in refractory chronic tophaceous cases.

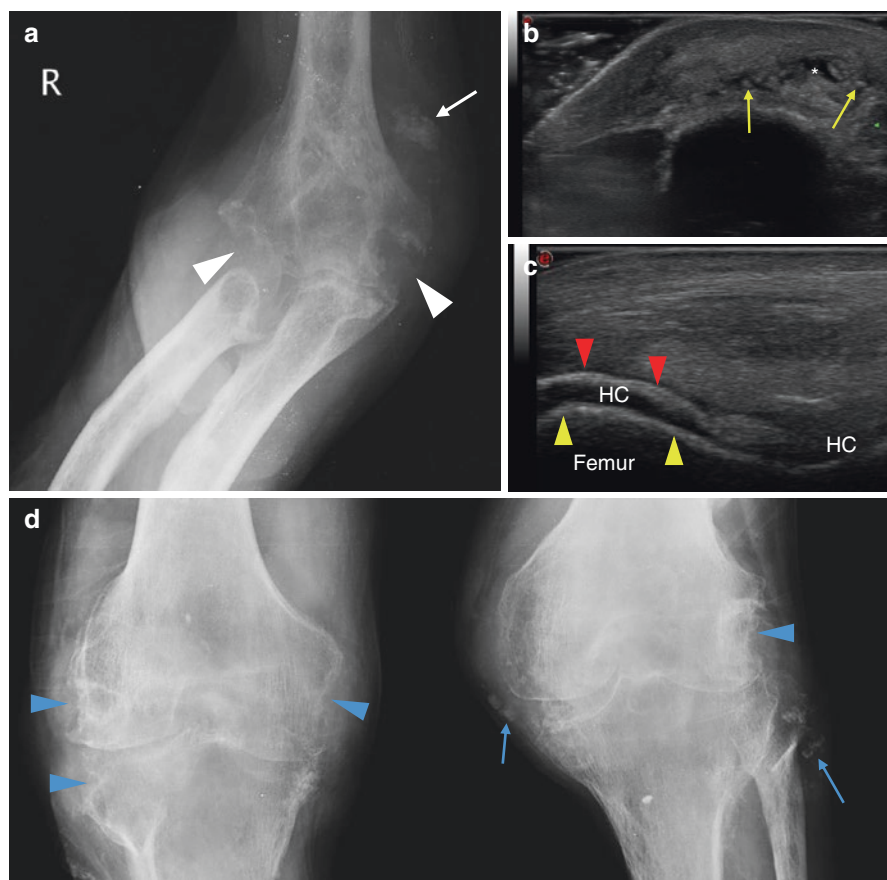


Fig. 12.6 Imaging findings in gout: elbow, knees

Elbows are frequently affected but usually the soft tissue is involved by the presence of swelling of the olecranon bursae (see Figs. 12.2d, e). Gout must always be considered in patients with unilateral olecranon bursitis. If bilateral, gout is usually the diagnosis. If the adjacent bone is involved, it may be either erosive or proliferative. In Fig. 12.6a, punched-out erosions with sclerotic borders involving the humeral condyles are seen (white arrowheads). Of note, the tophaceous deposit in the olecranon bursa (white arrow). MSUS (Fig. 12.6b) depicts olecranon bursitis in longitudinal view with a fluid filled bursa (*) and tophaceous deposits (yellow arrows).

Figure 12.6c shows the knee of a patient with the characteristic ultrasonographic finding “double-contour sign” (yellow arrowheads) in a transverse MSUS image of the suprapatellar knee joint. Two parallel hyperechoic contours on either side of the hypoechoic HC are clearly seen. The lower echogenic contour (yellow arrowheads) represents the femoral cortex, while the upper echogenic contour (red arrowheads) represents uric acid crystals accumulating on the surface of the hypoechoic HC.

In Fig. 12.6d, the knees of a patient with chronic tophaceous gout. Punched-out erosions of the femoral and tibial condyles are seen (blue arrowheads) with scattered periarticular tophaceous deposits (blue arrows).

Figure 12.6a and d are rare cases of gout patients without receiving the appropriate treatment.

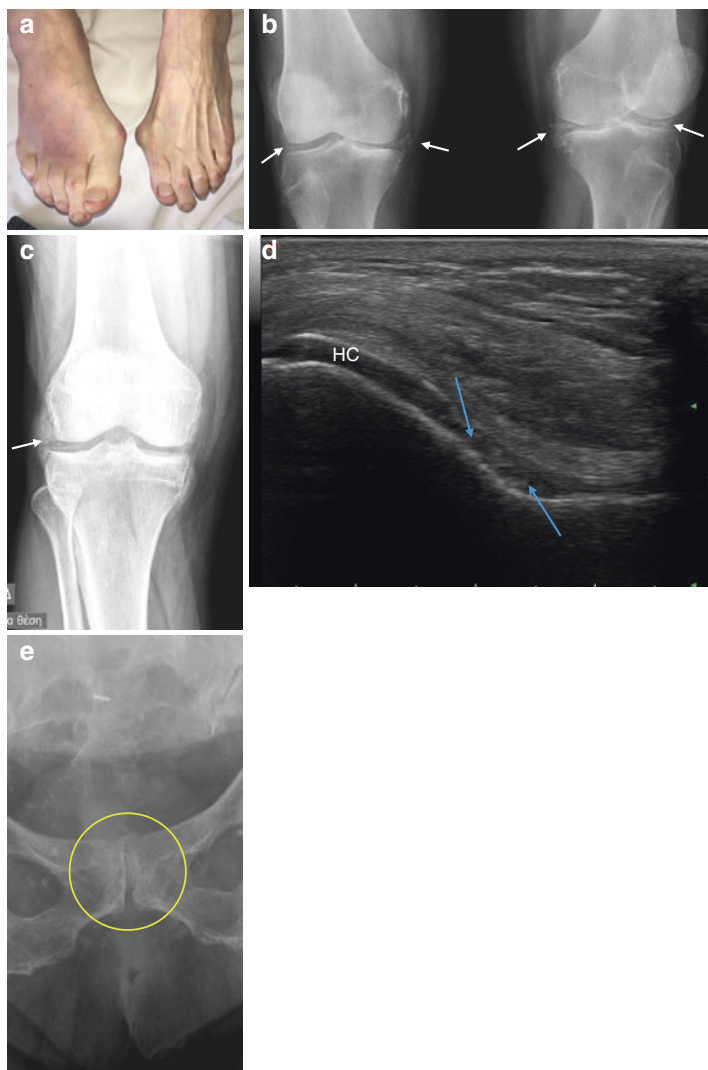


Fig. 12.7 Calcium pyrophosphate dehydrate crystal deposition disease

CPPD is observed more frequently with increasing age. Examination of the joint fluid reveals rhomboidal, weakly positively birefringent intra- and extracellular crystals of calcium pyrophosphate whereas in gout the joint fluid reveals needle-shaped, strongly negatively birefringent crystals of monosodium urate.

Figure 12.6a shows a patient 73-years old with a CPPD attack. The term chondrocalcinosis should be reserved for the radiological appearance of calcification of articular cartilage. There is marked redness and swelling of the right foot and the patient could not weight bear.

The typical clinical picture mimics acute urate gout, although it usually affects the wrist, knee or ankle. In Fig. 12.7b and c, there is chronic deposition of calcium pyrophosphate in the fibrocartilaginous menisci (white arrows) and in the HC. MSUS is a very useful imaging modality that helps identifying those deposits (Fig. 12.7d – blue arrows), because the HC of the knees is normally completely anechoic. Another site is the symphysis pubis (Fig. 12.7e – yellow circle). CPPD in the symphysis pubis is not a common finding.

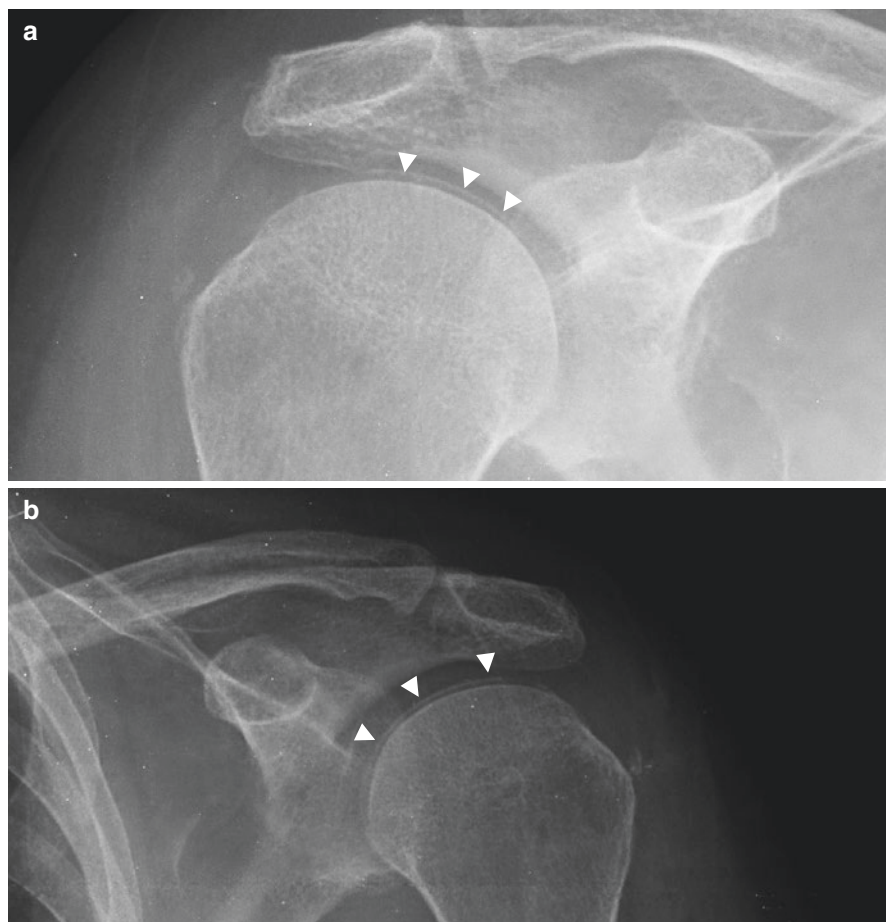


Fig. 12.8 Calcification of the hyaline cartilage

CPPD in the HC produces a fine line of calcification parallel to the surface of the bone as seen in Fig. 12.8a and b (humeral head – white arrowheads).

The knee joint is commonly affected. After the knee, the wrist is the second most commonly affected joint, with deposits usually appearing in the triangular ligament.

About 5% of patients with widespread chondrocalcinosis have a chronic inflammatory arthritis which mimics RA.

In younger patients who demonstrate symptomatic or even asymptomatic chondrocalcinosis on x-rays, associated diseases such as hyperparathyroidism, haemochromatosis or hypothyroidism should be excluded.

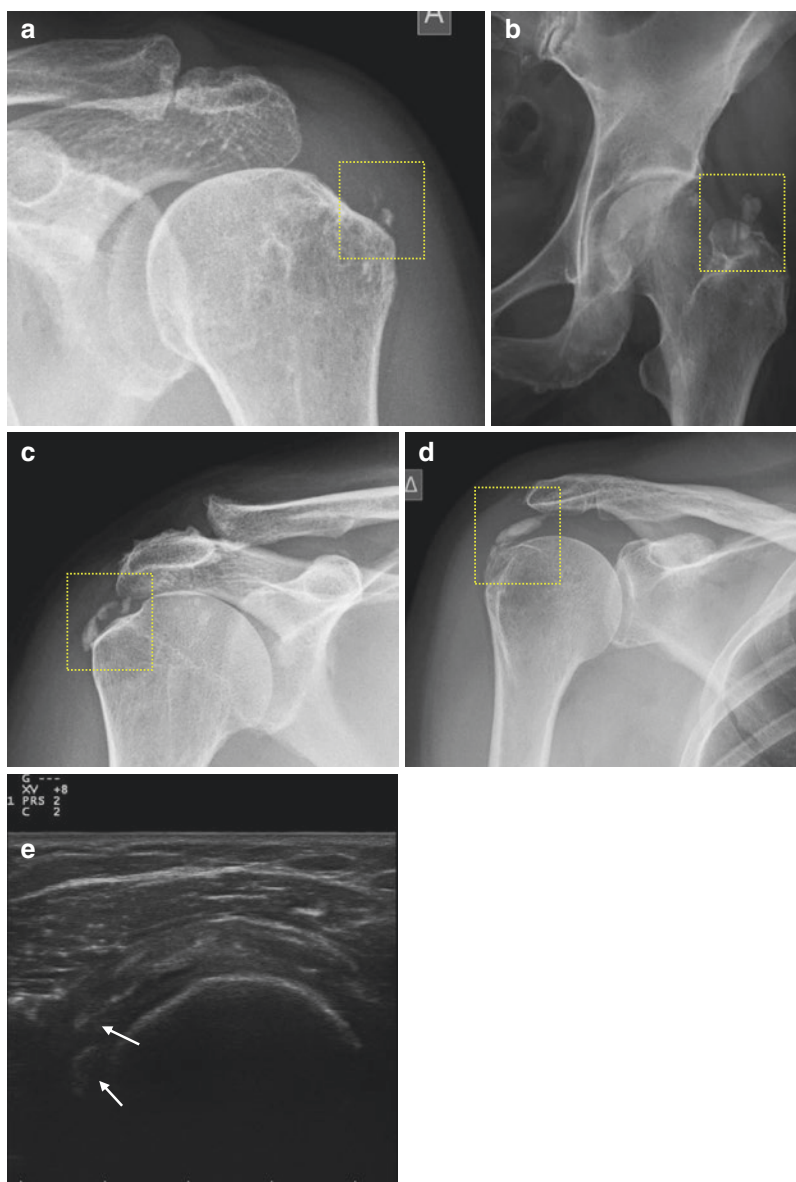


Fig. 12.9 Hydroxyapatite crystal deposition disease (HADD)

HADD is a disease with peri- and intra-articular deposition of hydroxyapatite or BCP crystals (yellow rectangles). Early deposition appears as a linear and poorly defined calcification often blending with the soft tissue (Fig. 12.9a), but by the time the depositions become as those in Fig. 12.9b–d. In the latter figures, there are well circumscribed, amorphous calcifications not containing trabeculae adjacent to the greater trochanter of the left femur and the greater tubercle of the right humerus respectively. This condition is very common and causes severe pain and functional disability of the affected joint. Figure 12.9e shows calcifications of the supraspinatus as seen by the use of MSUS (white arrows).

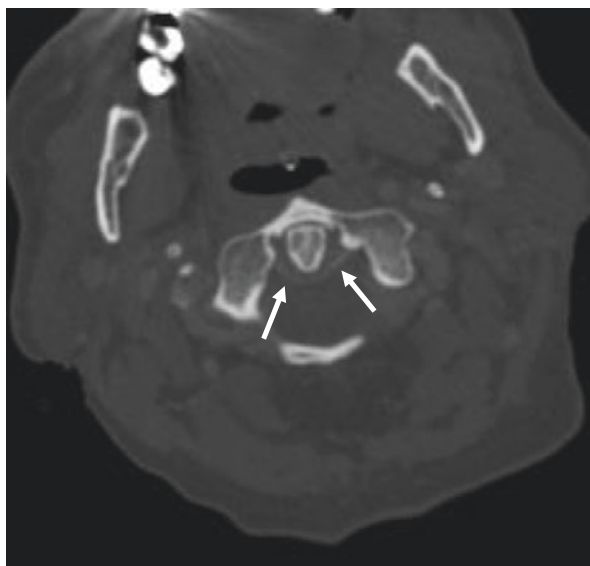


Fig. 12.10 Crowned dens syndrome

The “crowned” dens syndrome is the result of crystal deposition in the cruciform and alar ligaments surrounding the dens. It is a rare form of calcium crystal deposits and often presents with recurrent neck pain, stiffness of neck, increased inflammatory markers and fever. The typical image appears as a radiopaque “crown” around the odontoid process which is a curvilinear calcification of the transverse ligament of the atlas. In this CT scan you can notice the crystal deposition surrounding the dens (white arrows). This patient was admitted to the hospital due to localised pain at the back of the neck with neck stiffness and elevated inflammatory markers.

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Chapter 13

Osteoporosis



13.1 Introduction

Osteoporosis (OP) is a generalised metabolic bone disease characterised by insufficient formation or increased resorption of bone matrix, resulting in decreased bone mass and susceptibility to bone fractures. OP has a variety of possible causes and consequently manifests in a number of different forms, but the result is the same which is bone fracture. The basic distinction is between generalised or diffuse OP involving the vertebral bones, the femoral neck and wrists with different type of fractures. On the other hand, there is a localised OP to a simple region or bone which is called regional OP. This type of OP, particularly if accompanied by pain, frequently can masquerade as arthritis.

The most common form of localized OP is transient, regional OP. It affects the periarticular regions and has no definite aetiology such as trauma or immobilisation. Usually is a self-limited and reversible disorder of which three subtypes have been described.

13.2 Osteoporosis Types

- (a) Transient OP of the hip which is seen mainly in pregnant women and in young and middle age men. It affects the femoral head, neck and the acetabulum.
- (b) Regional migratory OP which affects the knee, the ankle and foot. It is seen mainly in men between the fourth and fifth decades of life. It is migratory characterised by severe pain and sometimes swelling around the affected joint.
- (c) Idiopathic juvenile OP is seen during or just before puberty and typically regresses spontaneously.

Other forms of regional OP are those related to inflammatory arthritides like rheumatoid arthritis (RA), psoriatic arthritis (PsA) etc. The types of OP are called periarticular or juxta-articular OP because they appear around of the inflamed joint. However, patients with inflammatory arthropathies may develop generalised or diffuse OP due to inflammation, immobilisation and the use of steroids.

The term OP originally referred to “porosis of bone” that contributes to bone’s failure to resist fracturing. The National Institute of Health (NIH) defines OP as a disease of compromised bone strength, resulting in an increased risk of fracture. Thus, OP, is both a disease and a risk factor for bone fracture. Bone strength reflects the combination of bone mass and bone quality. Bone mineral density (BMD) is used to assess OP. The World Health Organisation (WHO), defined OP as a BMD

greater than -2.5 standard deviations (SD) below the mean peak BMD in young healthy adults of the same gender, also known as T score.

13.3 Aetiology

The aetiology of OP is multifactorial and includes bone loss related to menopause and the consequence of ageing. Other causes include endocrine disorders like Cushing syndrome, hyperparathyroidism, hypogonadism, hyperprolactinaemia. Some other causes are the use of drugs like corticosteroids (CS), antiepileptics, antidepressants, haematological disorders (multiple myeloma), neurological disorders (stroke, Parkinson's disease) and chronic inflammatory disease like RA, spondyloarthritides (SpA), chronic obstructive pulmonary disease (COPD), systemic lupus erythematosus (SLE), sarcoidosis and others.

Ninety percent of all hip and spinal fractures are related to OP. Other sites of fractures include humerus, ribs, pelvis, ankle, and the clavicle. The clinical assessment of OP is to identify lifestyle risk factors for fracture. Thus, a careful past medical and family history to detect metabolic bone diseases is very important.

13.4 Diagnostic Modalities

Dual-energy x-ray absorptiometry (DEXA) is the most widely used method for accurate measurement of BMD. Plain radiographs are inaccurate for the assessment of BMD. Other skeletal modalities for OP comprise quantitative computed tomography (QCT) which is similar to DEXA in its ability to quantify the degree of bone loss. Another diagnostic modality is ultrasound (US) which is relatively insensitive for diagnosis of OP. Other diagnostic modalities used in OP are CT and magnetic resonance imaging (MRI) when indicated.

13.5 Management

The main goal of OP treatment is the prevention of fractures. Important considerations in bone health include adequate intake of calcium and vitamin D, avoidance of cigarette smoking and alcohol abuse as well as regular weight-bearing exercise. Medications used to treat OP include bisphosphonates, selective estrogen-receptor modulators, parathyroid hormone and denosumab, a selective inhibitor of RANKL (receptor activator of nuclear factor kappa-B ligand).

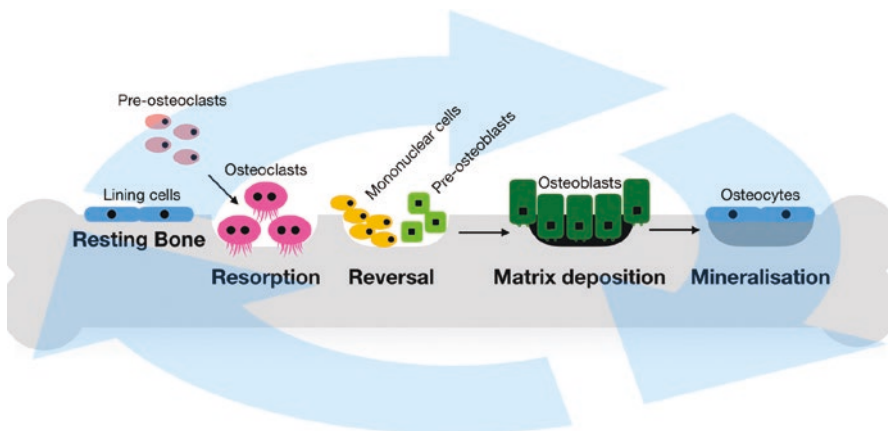


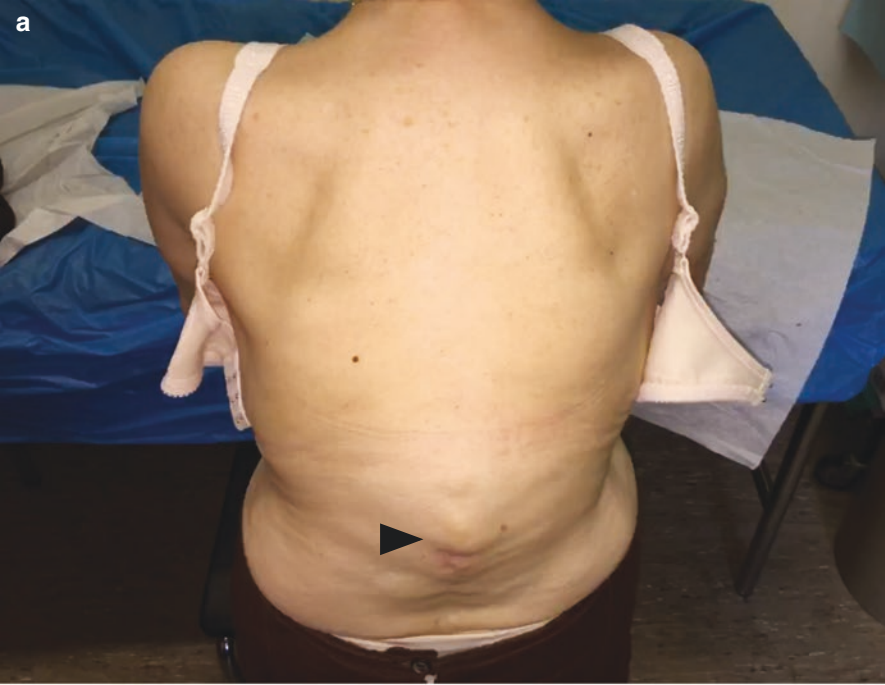
Fig. 13.1 Bone remodeling

Throughout adult life, bone is continuously being turned over. This leads to the renewal of bone tissue, maintaining the biomechanical properties of the skeleton. Osteoblasts and osteoclasts are the major bone cells involved in bone remodeling. Osteoblasts synthesize bone matrix and lead to its mineralization whereas osteoclasts are responsible for bone resorption. There are distinct phases in bone remodeling which are shown in this figure. First, there is a phase of activation with the pre-osteoclasts to proliferate and differentiate into mature osteoclasts. Then resorption occurs. This is the second phase where osteoclasts will excavate an erosion cavity the so-called “Howship’s lacuna”. The reversal phase follows, during which mononuclear cells prepare the bony lacunae for the next step. At this stage, pre-osteoblasts proliferate and differentiate into mature osteoblasts. During the phase of bone formation, the osteoblasts synthesize layers of osteoid matrix which are mineralized subsequently.

Fig. 13.2 Gibbus deformity

Gibbus deformity is a short-segment structural thoracolumbar kyphosis resulting in sharp angulation. A number of causes can produce this deformity and compression fractures due to OP are among these causes.

In Fig. 13.2a, a female patient with gibbus deformity of the L1-L2 is shown whereas in Fig. 13.2b a male patient with a gibbus deformity of the T11-T12 is depicted (black arrowheads).



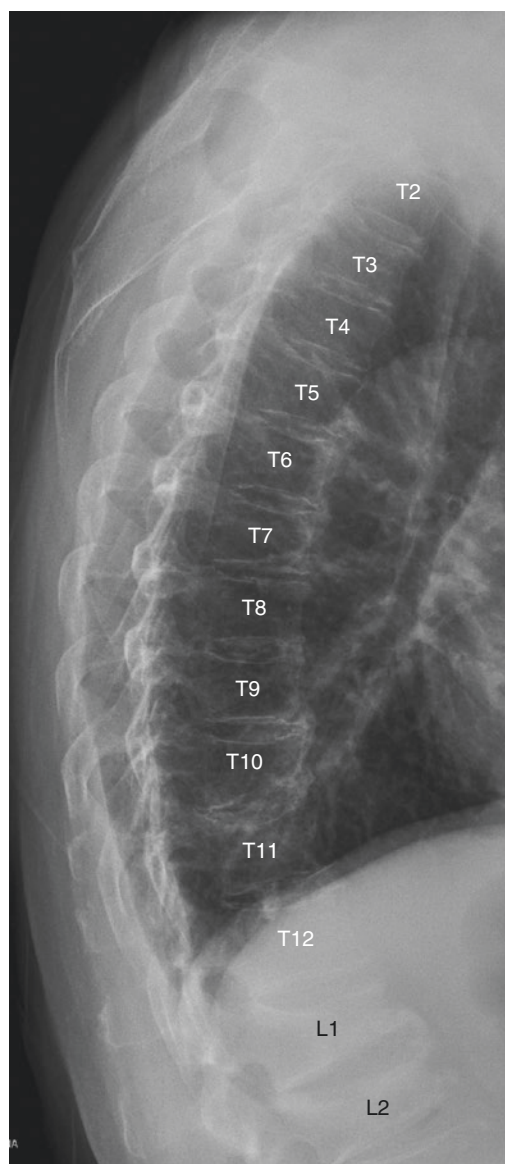


Fig. 13.3 Compression fractures

Compression fractures could appear after trauma or in osteoporotic patients. There are four main types of compression fractures: (a) burst fractures, (b) wedge fractures, (c) osteoporotic spinal compression fractures, (d) vertebra plana. Osteoporotic spine fractures can be graded based on the vertebral height loss as: (a) mild (20–25%), (b) moderate (25–40%), (c) severe (>40%). This x-ray is from a 74-year old patient with known OP. She had a low bone mineral density and a T-score of -4.1 of the lumbar spine. She developed vertebral fractures of the L1 and L2 vertebrae after sitting on a chair. This is a moderate to severe osteoporotic spine fracture as the height of the vertebrae is approx. 40% less than the above vertebra. Patients with severe OP, can develop this kind of fractures even with the minimal axial load.

Fig. 13.4 Compression fractures – wedge fractures
Wedge fractures are very common in patients with OP. Anterior compression of the vertebral body is the characteristic feature of this kind of fracture (posterior intact/less affected, wedge shape). Usually stable but can lead to deformity such as kyphosis of the spine (especially when more than one occur). The patient in Fig. 13.4 has multiple compression fractures (white arrows). Typical wedge fractures are marked with an asterisk.

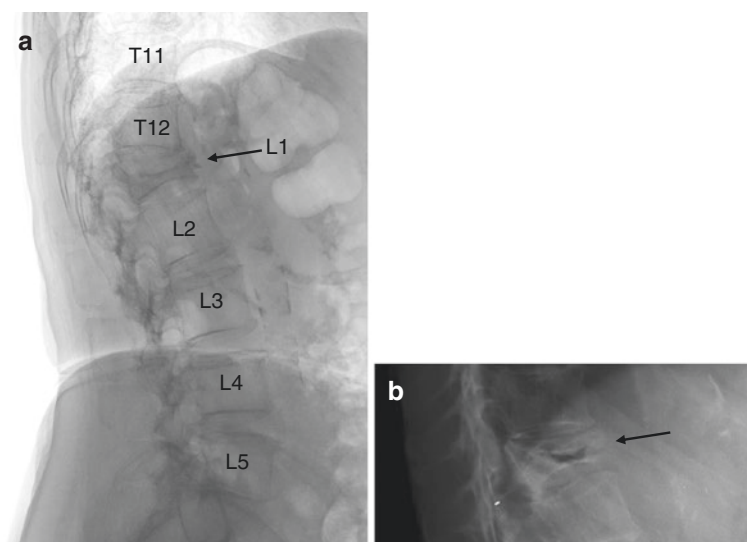
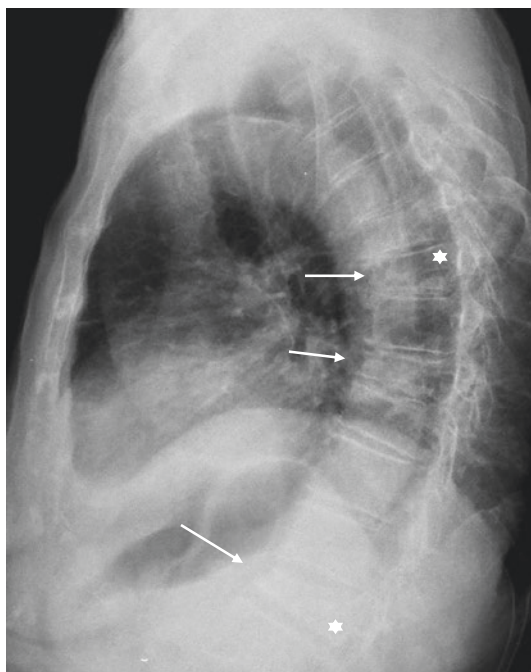


Fig. 13.5 Compression fractures - Vertebra plana

When a vertebral body loses almost its entire height anteriorly and posteriorly it is called vertebra plana. The most common cause of this type of fracture is trauma followed by OP. Other causes include Langerhans cell histiocytosis (most common cause in children), osteogenesis imperfecta, leukaemia, vertebral metastases, and multiple myeloma. In Fig. 13.5a and b two different patients with an osteoporotic fracture of the L1 and T12 vertebral bodies (black arrow) respectively are shown.

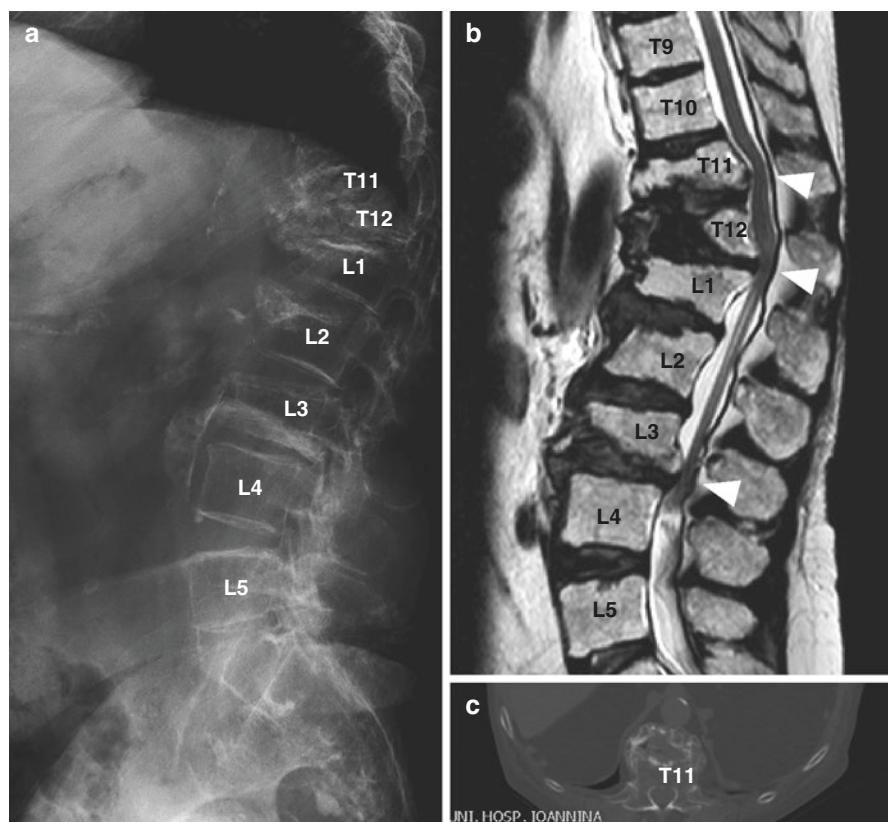


Fig. 13.6 Multiple vertebral fractures of the thoracolumbar spine

Radiography, comprising of anteroposterior (AP) and lateral views of thoracolumbar spine, is the cornerstone for detecting vertebral fractures. AP views are generally obtained once at baseline. Lateral radiographs are sufficient for follow-up and serial assessment. Most compression fractures occur at T7-T8 and T12-L1 regions, thus it is important to assess the mid-dorsal and the thoracolumbar regions.

CT, because of its superior ability to depict bone as compared to radiographs, can also better detect cortical bone destruction and involvement of posterior elements of spine thus distinguishing benign from malignant fractures and acute versus chronic fractures. However, despite the ease of identifying vertebral fractures in CT, many fractures still don't get reported because of assessment of vertebrae in axial sections only instead of sagittal sections.

Plain radiograph (Fig. 13.6a) and MRI (Fig. 13.6b) of a female patient 62-years old with multiple osteoporotic fractures of the thoracolumbar spine (T11, T12, L1, L2, L3). Note that MRI shows also significant compression of the spinal canal at multiple sites (white arrowheads). In Fig. 13.6c an axial unenhanced CT image obtained at the level of the T11 vertebral body of the same patient shows the fractured vertebral body.

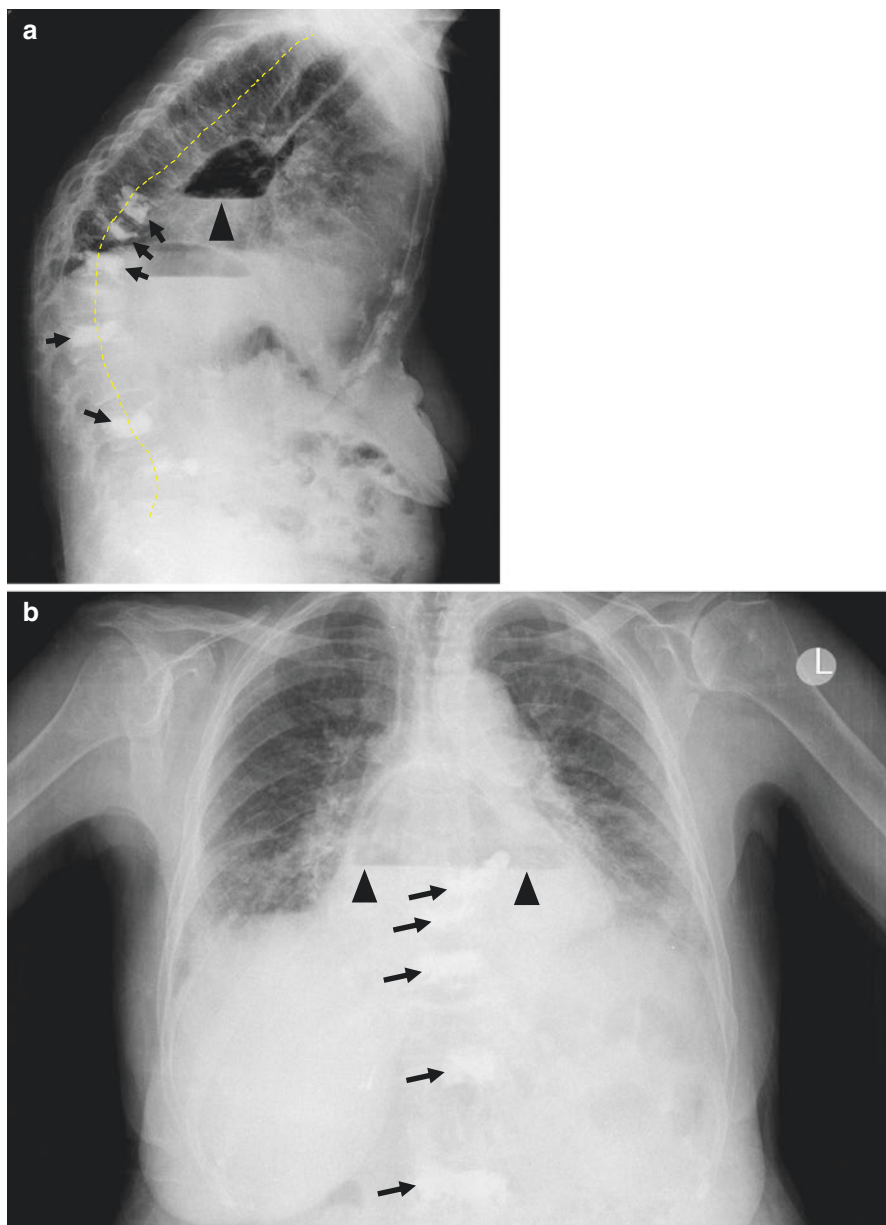


Fig. 13.7 Vertebroplasty for vertebral compression fractures

Vertebroplasty was commonly employed to treat symptomatic vertebral compression fractures refractory to conservative treatment. These procedures involve the percutaneous injection of bone cement, usually polymethyl-methacrylate, into the fractured vertebral body. Nowadays, it is not routinely used as new medicines have emerged but it is still offered to selected patients. This is a 78-year old patient with long-standing RA and multiple fractures due to CS. In Fig. 13.7a and b, note the radio-opaque cement within the fractured vertebrae (black arrows) and a large hiatal hernia with an air-fluid level within it (black arrowheads). Due to the multiple vertebral fractures note the kyphosis of the spine (yellow dashed line).

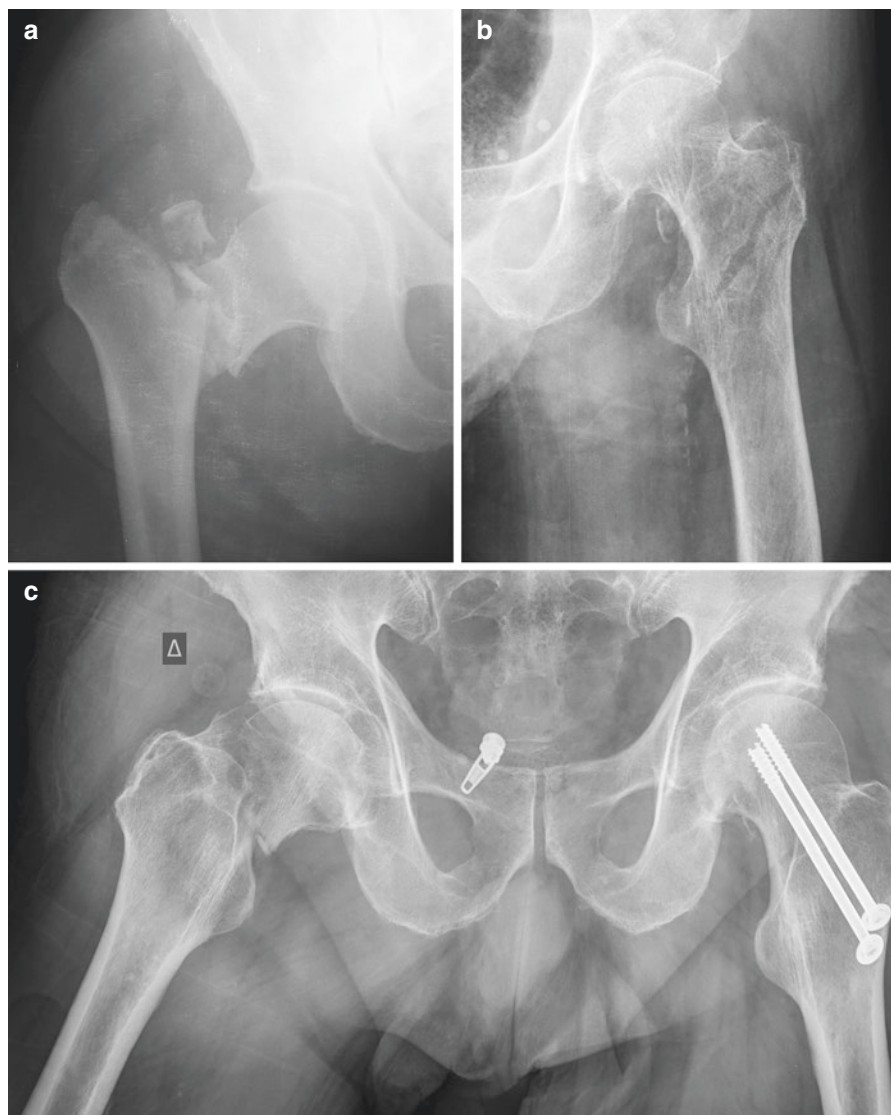


Fig. 13.8 Neck of femur fracture due to osteoporosis

Neck of femur (NOF) fractures are common injuries among older patients, especially elderly osteoporotic women. A reduced bone mineral density predisposes to this kind of fracture. In Fig. 13.8a and b, typical NOF and intertrochanteric fractures are shown respectively. The same in Fig. 13.8c (NOF), but as you can note, this patient had already a NOF fracture of the contralateral femur which was treated surgically.

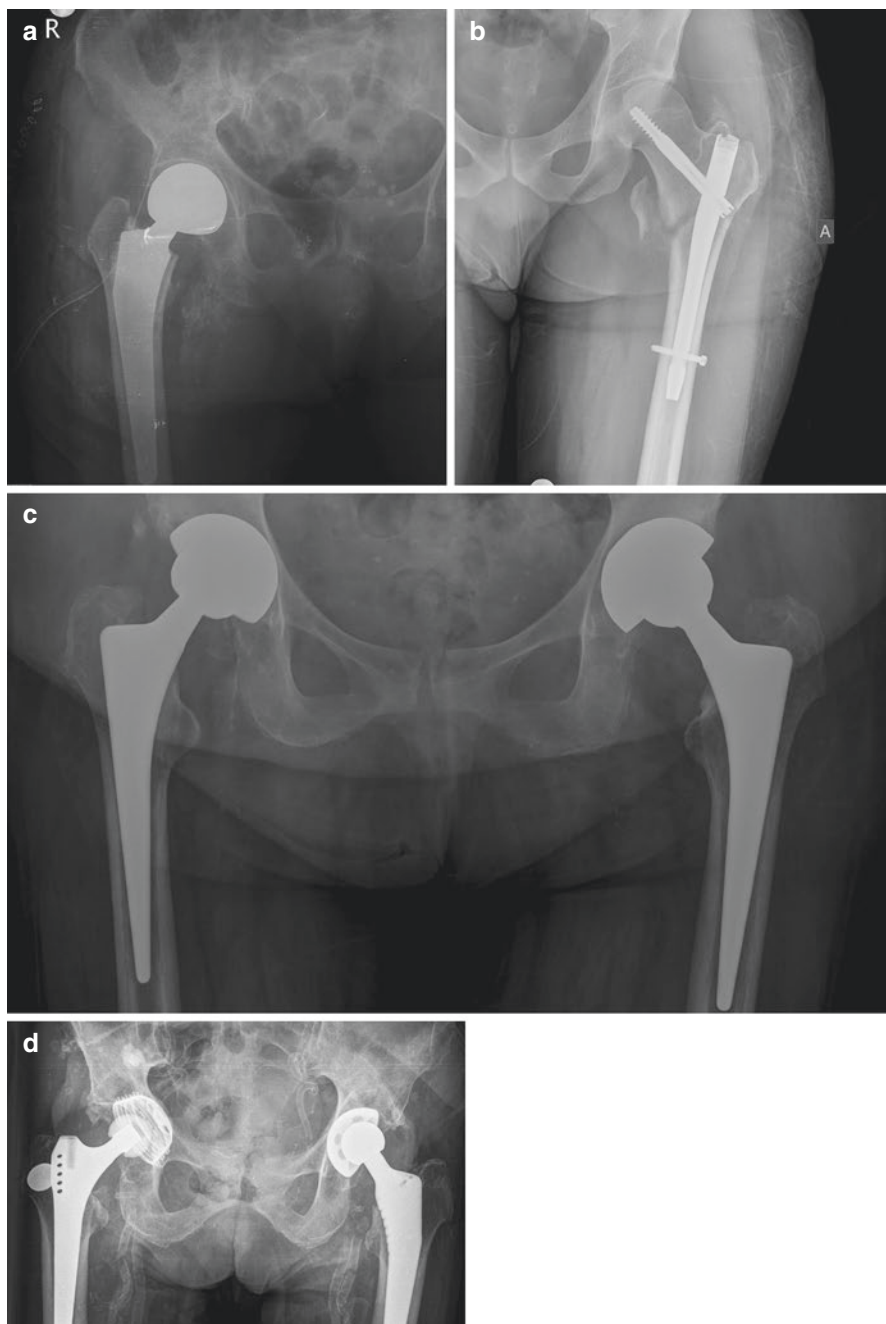
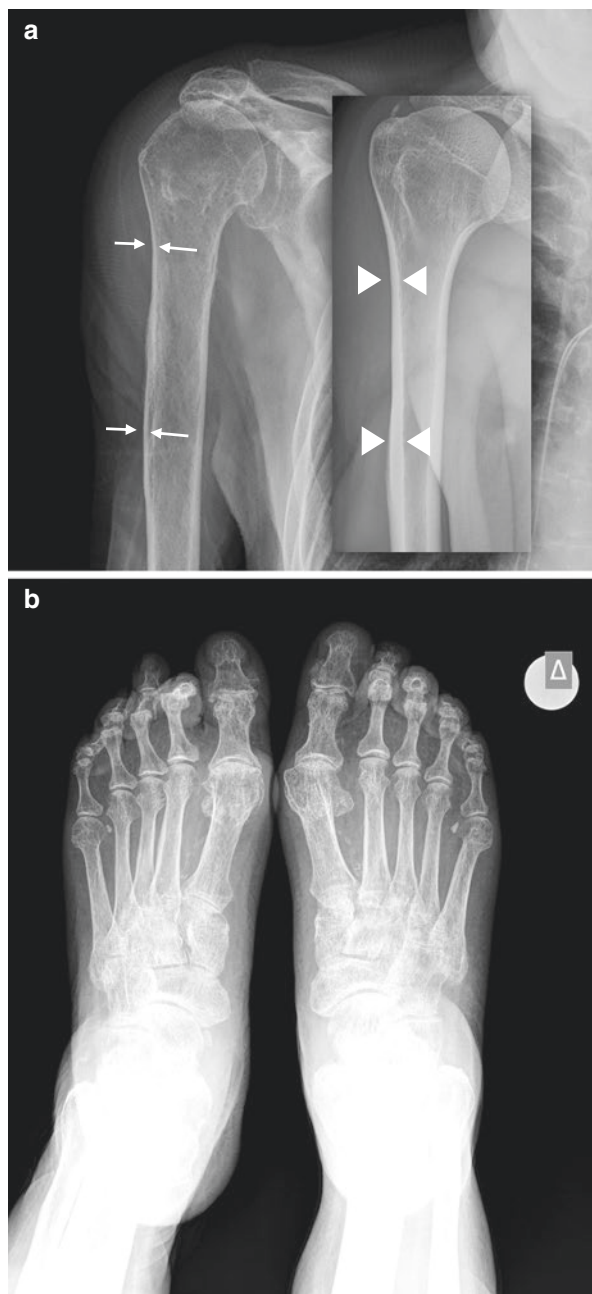


Fig. 13.9 Neck of femur and intertrochanteric fractures due to osteoporosis

In Fig. 13.9a–d, a hemiarthroplasty (HAP), an intra-medullary hip screw and, two total hip arthroplasties (THA) are shown respectively. Hip repair due to a fall in an osteoporotic patient is one of the commonest surgical procedures in the elderly. THA is preferred when the joint has also been damaged by osteoarthritis (OA).

Fig. 13.10 Osteoporosis
Plain radiography is not a sensitive diagnostic modality for OP, as more than 40–50% bone loss is required to appreciate decreased bone density on radiograph. A decreased cortical thickness and loss of bony trabeculae are early stages in radiography. In Fig. 13.10a the humeral cortical bone is decreased in comparison with an x-ray of a healthy person in the inset figure (white arrows vs white arrowheads). Note also that the bony trabeculae are visible in the head of the inset figure in comparison with the osteoporotic patient. In Fig. 13.10b, diffuse osteopenia is evident with decreased cortical bone and decreased radio-density of the radiograph. The decreased cortical bone thickness is best seen at the diaphysis of the metatarsophalangeal (MTP) bones.

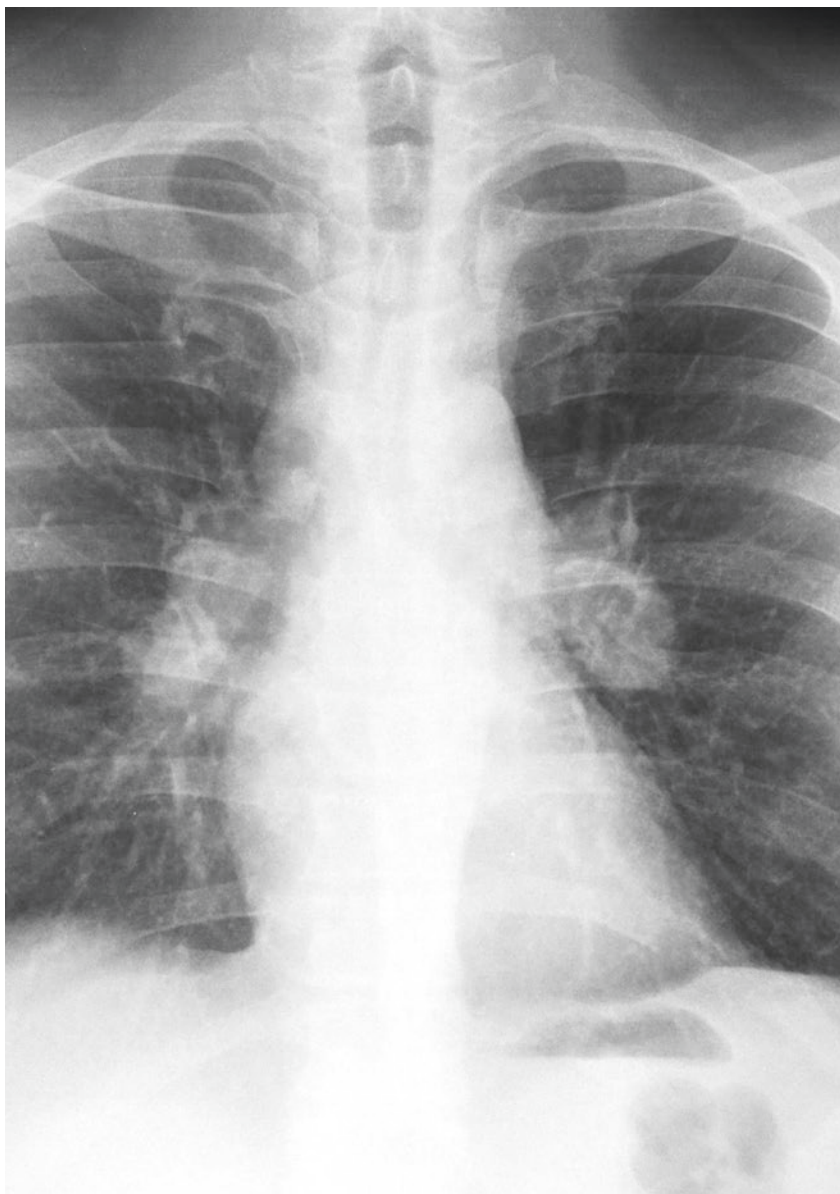


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Chapter 14

Sarcoidosis



14.1 Introduction

Sarcoidosis is a chronic, systemic inflammatory disorder characterised by the presence of epithelioid non-caseating granulomata in the affected organs. The lungs are affected in about 90% of the cases, and pulmonary disease accounts for most of the morbidity and mortality associated with sarcoidosis. Virtually every organ of the body can be affected like the liver, skin, eye etc. The features of granulomata are not specific for sarcoidosis and other conditions known to cause granulomata must be excluded. These conditions include mycobacterial and fungal infections, environmental agents such as beryllium, malignancy and others.

14.2 Epidemiology

The disease affects young adults in the second and third decade of life. Sarcoidosis has a worldwide distribution with the highest prevalence in northern European countries. Epidemiological studies on sarcoidosis show significant heterogeneity in incidence, prevalence, disease presentation, disease characteristics, severity and prognosis, among different ethnic and racial groups. Sarcoidosis seems to be 3–4 times more common in blacks than whites. In USA it is more common in the African-American population and in Europe in the northern European countries.

14.3 Aetiopathogenesis

The aetiology of the disease is unknown. Any tissue of the body can be affected by sarcoidosis with the characteristic formation of granulomata. In the lungs, the initial lesion is alveolitis, consisting of Th1 CD4⁺ cells as well as alveolar macrophages which are upregulated producing a variety of cytokines such as interleukin (IL)-2, IL-12, IL-18, TNF α and interferon (IFN)- γ . The cooperation of this CD4⁺ and macrophages in the presence of cytokines contributes to the formation of granulomata.

14.4 Clinical Manifestations

Sarcoidosis typically involves more than one organs. Pulmonary involvement is present in about 90% of cases. Skin and eye manifestations account for 20–30% of cases, musculoskeletal about 10–20% while other organs are affected less frequently.

Pulmonary manifestations: in about 50% of cases of lung involvement, sarcoidosis is detected incidentally by pulmonary abnormalities in routine chest radiography. Presenting symptoms may be non-specific and include dry cough, dyspnoea, and chest pain. Lung auscultation usually is normal, however as the disease progresses crackles or rales are heard on auscultation of the lungs. Sarcoidosis is usually self-limited and tends to go into remission in about 70–80% of the cases. While Computed Tomography (CT) scan of the chest is more sensitive to detect lung abnormalities, the standard scoring system described by Scadding in 1961 for chest radiography, remains the preferred method for staging lung involvement in sarcoidosis. Stage I: bilateral hilar adenopathy without parenchymal involvement. Stage II: bilateral hilar adenopathy with parenchymal infiltrates. Stage III: dense parenchymal infiltrates without adenopathy. Stage IV: pulmonary fibrosis.

About half of patients present with bilateral hilar adenopathy as the first expression of sarcoidosis (stage I). In about 70–80% of patients with stage I sarcoidosis, there is a regression of hilar adenopathy within 1–3 years.

Skin manifestations: are identified in about 20–30% of the cases. The classic cutaneous lesions include: erythema nodosum (EN), maculopapular lesions, hyper- and hypopigmentation, keloid formation and subcutaneous nodules. Such lesions occur over the extensor surfaces of the arms, forearms and legs, and tend to resolve with scarring and retraction.

Two specific clinical presentations may occur. First, Löfgren's syndrome consists of fever, EN, bilateral hilar adenopathy, uveitis and symmetric polyarthritis. This is an acute clinical manifestation more common among Scandinavians. Second, lupus pernio which is a confusing name, refers to a particular type of sarcoidosis skin lesion that occurs on the face and scalp. These lesions appear as violaceous plaques found on the nose, nose alae, malar areas, eyelids and scalp. These lesions are chronic and indolent, difficult to be treated.

Eye manifestations: a significant number of patients with sarcoidosis has eye manifestations. Sarcoidosis lesions can involve all major compartments of the eye including anterior and posterior uveitis, retinitis and pars planitis. Symptoms include photophobia, blurred vision, increasing tearing or eye dryness. In these cases, a differential diagnosis of Sjögren syndrome (SS) should be considered. There are some asymptomatic patients who have active inflammation and may develop blindness. Therefore, it is recommended that all patients with sarcoidosis receive a detailed ophthalmological examination.

Joint involvement accounts for 10–20%. As mentioned above frank arthritis tends to occur in patients with acute presentation of sarcoidosis (Löfgren's syndrome). Arthralgias occur commonly in patients with acute sarcoidosis, but chronic arthritis is uncommon. Chronic arthritis includes dactylitis characterised by violaceous swelling involving the second and third fingers, non-deforming arthritis with granulomatous synovitis, non-erosive joint deformity (Jaccoud's-like arthropathy). Most commonly involved joints are the hands, ankles, knees, wrists and shoulders. Cystic punched-out lesions are commonly observed on plain radiography or other imaging studies, located in the bones at the hands, feet, pelvis, and skull.

Neurological manifestations occur in about 5% of patients with sarcoidosis. Some common forms are cranial neuropathies (especially neuritis and facial palsy), followed by encephalopathy or myelopathy associated with enhancing lesions on Magnetic Resonance Imaging (MRI). Another neurological manifestation of sarcoidosis is peripheral neuropathy with sensory and motor manifestations.

14.5 Diagnostic Approach

Diagnosis of sarcoidosis requires the involvement of two or more organs with the presence of non-caseating granuloma. As it is mentioned above, the presence of granulomata is not a specific finding for sarcoidosis. Therefore, many other diseases must be excluded. These diseases include fungal and mycobacterial infections, malignancies, beryllium, trauma etc. There are no specific diagnostic tests for sarcoidosis. Its diagnosis rests on a combination of the following: (a) compatible clinical and radiographic manifestations, (b) histological proof of non-caseating granulomata, (c) exclusion of other diseases with similar presentation.

Thus, some laboratory and imaging tests may be helpful for its diagnosis. Serum levels of angiotensin converting enzyme (ACE) may be increased in patients with sarcoidosis. However, the test has somewhat low sensitivity and specificity, since it is found also in other diseases such as milliary tuberculosis, disseminated granulomatous infections, leprosy, Gaucher disease and others.

The CT scan is being used frequently for the exposure of interstitial lung disease. The presence of adenopathy and a nodular infiltrate is not specific for sarcoidosis. Gallium 67 scanning has been used out to detect inflammatory activity in various parts of the body. More recently the positron emission tomography (PET) scan, using radiolabeled fluorodeoxy-glucose as a marker has provided useful information about inflammatory activity in patients with sarcoidosis.

14.6 Management

Treatment of sarcoidosis depends on clinical manifestations. In patients with limited cutaneous disease or Löfgren's syndrome non-steroidal anti-inflammatory drugs (NSAIDs) or small doses of corticosteroids (CS) may be sufficient to combat symptoms. Patients with critical organ involvement like lung, heart, central nervous system and others, high doses of steroids and immunosuppressive drugs are used (cyclophosphamide – CP, azathioprine - AZA, methotrexate - MTX). In resistant cases infliximab has been also used.

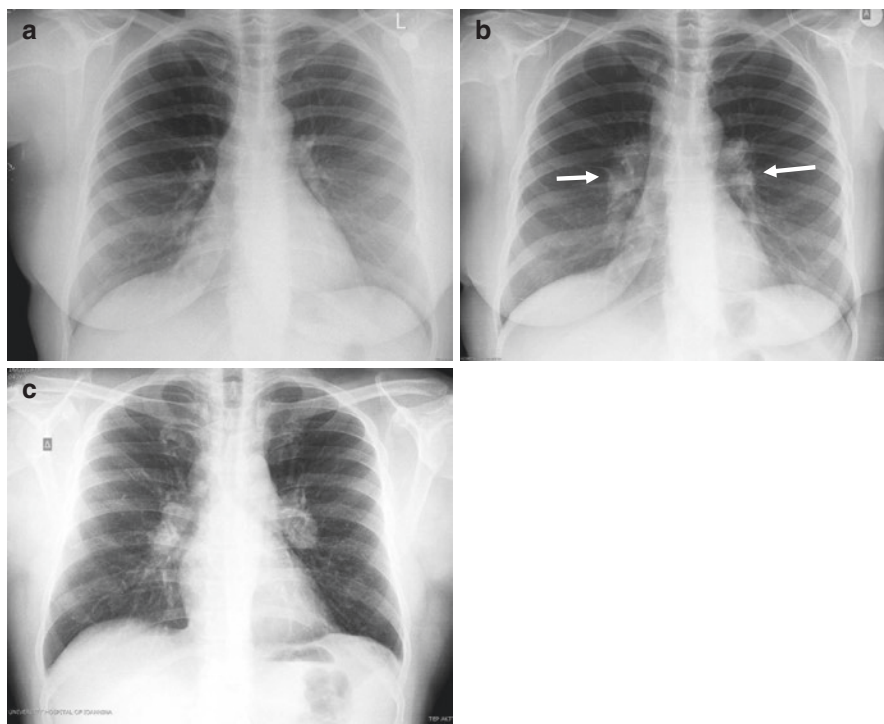


Fig. 14.1 Radiographic manifestations of Sarcoidosis – Pulmonary sarcoidosis

Thoracic involvement is common in sarcoidosis and accounts for most of the morbidity and mortality associated with the disease. Approximately 90% of patients with sarcoidosis will develop thoracic radiologic abnormalities at some stage whereas 20% will develop chronic lung disease leading to pulmonary fibrosis. Chest radiography may reveal pulmonary sarcoidosis on a routine check, especially when no other systemic manifestations are present. Except from the Scadding classification system of radiographic pulmonary sarcoidosis which has 4 different Stages, it can be also staged with the Siltzbach classification system into five stages: Stage 0, normal chest radiograph; Stage 1, lymph node enlargement (50% at time of diagnosis); Stage 2, lymph node enlargement and pulmonary opacities (30% at time of diagnosis); Stage 3, pulmonary opacities only; and Stage 4, pulmonary fibrosis.

Figure 14.1a and b (3 years later) are from the same patient with Stage 0 and Stage 1 pulmonary sarcoidosis respectively. You can notice the bilateral hilar lymph node enlargement (white arrows) in comparison with the normal first chest radiograph. This patient was a 49-year old female who attended the emergency department with fever, polyarthralgias, EN and dyspnoea. The diagnosis was Löfgren's syndrome (see Fig. 14.3 for the dermatologic manifestations of the same patient).

Figure 14.1c shows a male patient with Stage 1 pulmonary sarcoidosis who was asymptomatic but had a chest radiograph prior to a surgical operation. This was an incidental finding in which large hilar lymphadenopathy is present.

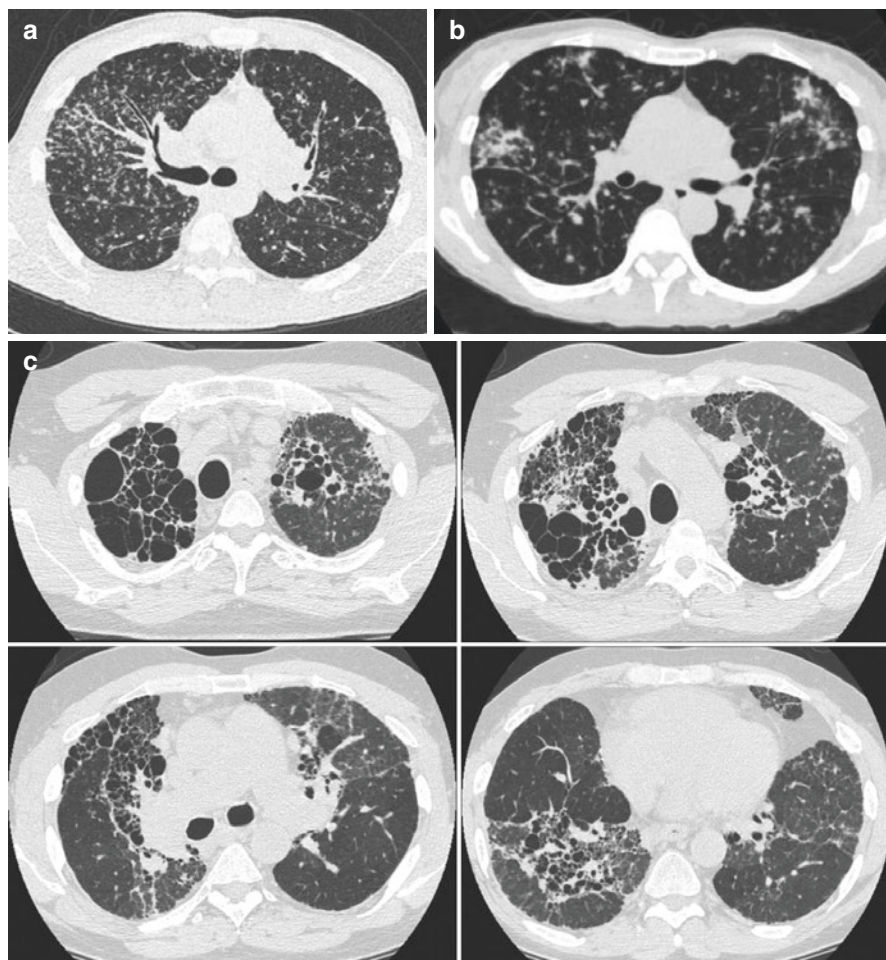


Fig. 14.2 Computed Tomography in Sarcoidosis

Although chest radiography is often the first diagnostic imaging study in patients with pulmonary involvement, CT is more sensitive for the detection of adenopathy and subtle parenchymal disease. Pulmonary sarcoidosis may manifest with various radiologic patterns as shown in the CT images above.

Figure 14.2a high-resolution (HR)CT multiple peribronchial and perilymphatic nodules in the middle and lower pulmonary fields with thickening of the bronchial wall.

Figure 14.2b scattered, confounding micronodular lesions in the middle and lower pulmonary fields with thickening of the interlobular septae.

Figure 14.2c extensive lesions of pulmonary fibrosis mainly in the upper and middle pulmonary fields with destruction of the pulmonary parenchyma and cyst formation. Note also the perihilar lymphadenopathy.

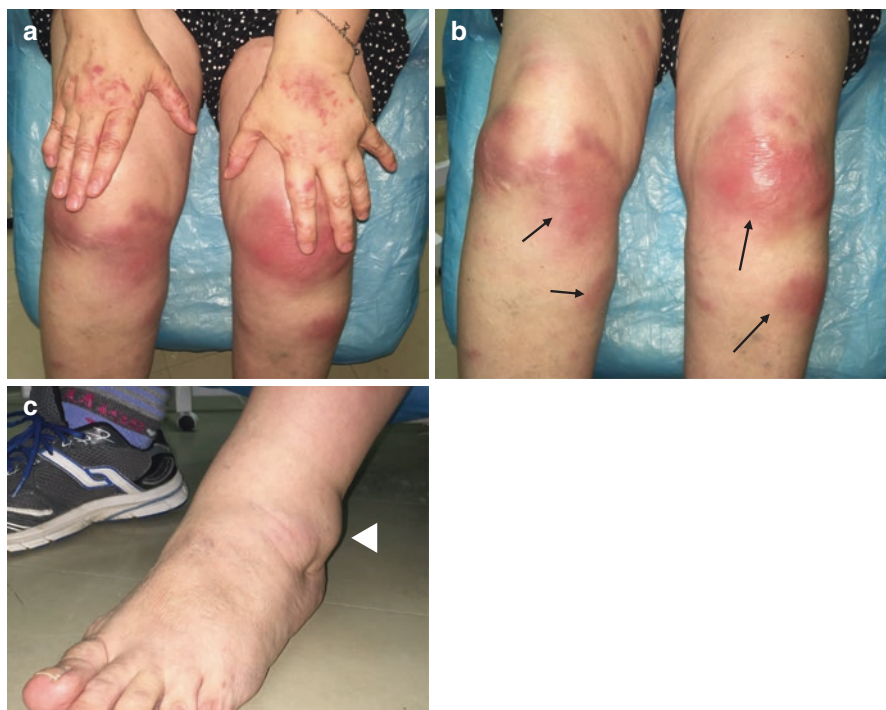


Fig. 14.3 Cutaneous manifestations of Sarcoidosis

Löfgren's syndrome is an acute variant of sarcoidosis with excellent prognosis and it is characterised by the triad of EN, bilateral hilar adenopathy, and arthritis or arthralgias.

In Fig. 14.3a, b and c maculopapular rash at the extensor surface of the hands is seen with EN and periarticular ankle inflammation respectively. The chest radiograph is seen in Fig. 14.1b.

Some authors recognise a variation of Löfgren's syndrome that presents with periarticular ankle oedema (Fig. 14.3c – white arrowhead) with bilateral hilar adenopathy. This variant may or may not present with EN.

EN (black arrows) is usually present below the knees but it can be found also in other sites.

The treatment of most patients with Löfgren's syndrome is conservative, with the use of NSAIDs and sometimes bed rest. CS are sometimes needed. The prognosis of patients with Löfgren's syndrome is excellent, with a higher remittance rate and a lower relapse rate than in those with sarcoidosis.



Fig. 14.4 Erythema nodosum

Dermatologic manifestations are seen in 25% of patients. EN is the most common form of panniculitis. It may have many aetiological factors. Among them, streptococcal infections, tuberculosis, connective tissue disorders, oestrogen intake, pregnancy and others. It occurs 3–5 times more often in female patients. EN appears as painful rounded nodules, located most often on the anterior surface of the lower extremities. Sarcoidosis is the second most common cause of EN. This is a patient with pulmonary sarcoidosis and EN. Multiple erythematous lesions which coalesce and form plaques are seen on the anterior surface of both limbs.

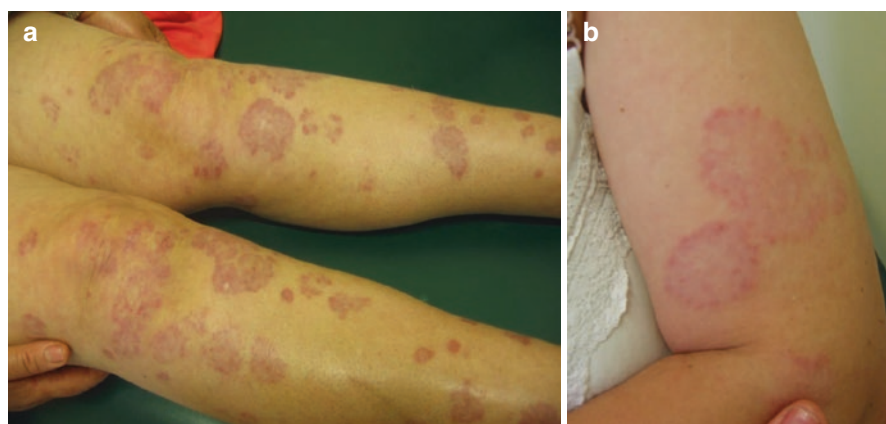


Fig. 14.5 Vasculitic manifestations of Sarcoidosis – Cutaneous annular sarcoidosis

Annular lesions in sarcoidosis are not uncommon. These are two different patients that presented with multiple annular lesions on the lower (Fig. 14.5a) and upper (Fig. 14.5b) extremities. These lesions appear as various-sized annular eruptions on the lower extremities. Note the slightly elevated erythematous border and hypopigmentation in the central areas. Some lesions coalesced to form irregular-shaped areas of erythema. Histology revealed granulomatous vasculitic lesions.

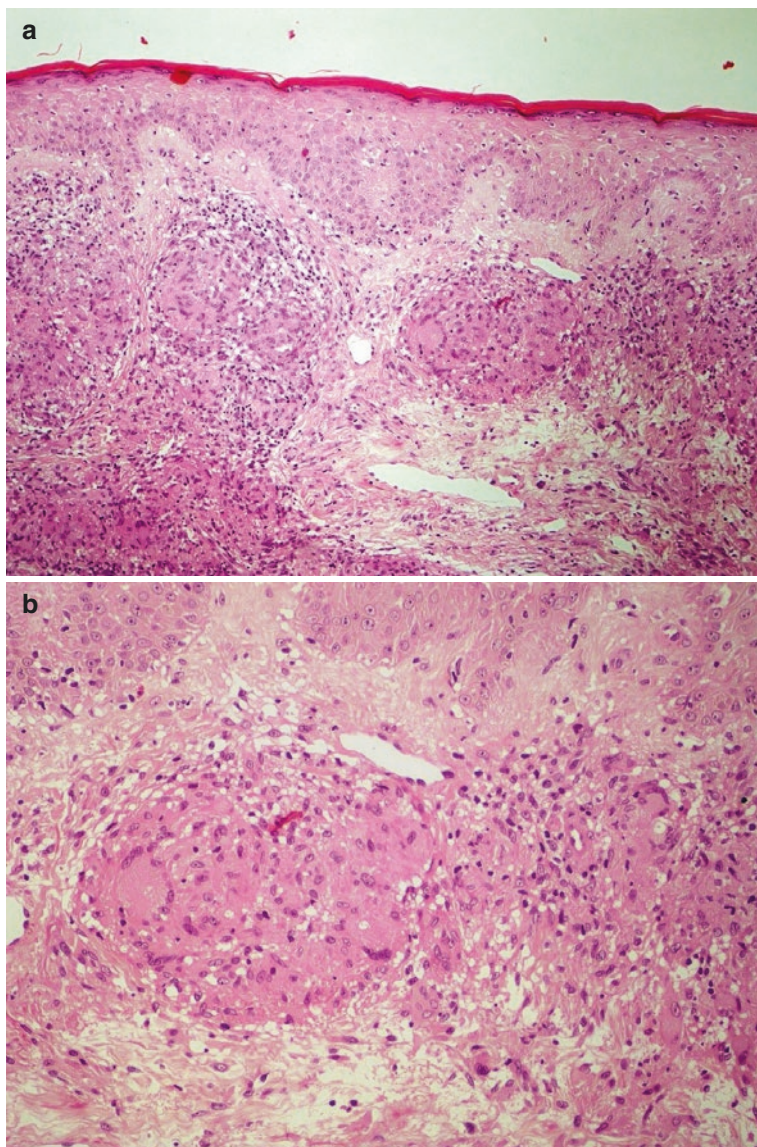


Fig. 14.6 Histologic features

Figure 14.6a discrete or crowded granulomas throughout the dermis (H-E $\times 100$).

Figure 14.6b sarcoidal granulomas: collections of epithelioid histiocytes some of them multinucleated, surrounded by mild infiltrates of lymphocytes. Asteroid or Schaumann bodies observed within some histiocytes (H-E $\times 200$).

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Chapter 15

Miscellaneous Conditions



15.1 Relapsing Polychondritis

15.1.1 Introduction

Relapsing polychondritis (RP) is an uncommon disorder of unknown aetiology which is at the crossroad between auto-inflammatory and autoimmune diseases. It is characterised by recurrent inflammation of cartilaginous structures throughout the body especially of the ears, nose, eyes and tracheobronchial tree. It was described by Jaksch-Wartenhorst as a polychondropathia in 1923 while Pearson et al. coined the term RP in 1960. It has a variety of clinical manifestations affecting many organs and systems, including joints, heart, kidney, skin and others. RP may occur alone and then it is described as primary or can be associated with other conditions characterised as secondary RP.

15.1.2 Epidemiology

It is a rare disorder that affects both genders equally. The peak incidence is between the fourth and fifth decade, but it also may occur in children and older adults. No ethnic or familial clustering has been reported. There is an association with the human leukocyte antigen (HLA)-DR4. The association of RP with other autoimmune or systemic diseases has been found to be approximately 25–30%.

15.1.3 Clinical Manifestations

The onset is usually abrupt and relapses occur in the course of the disease. The most common clinical manifestation is inflammation of the auricular portion of the external ear which can be unilateral in most of the cases or even bilateral. As the cartilage matrix is destroyed and the inflammatory process of the auricular portions continues, the ear becomes flabby. Furthermore, other structures of the ear can be affected. The Eustachian tubes may close, leading to hearing loss and recurrent otitis. Ear involvement occurs in about 50–60% of the patients, followed by inflammation of the nasal cartilage which is the second most common site involved. There is pain, local tenderness and as the disease progresses, saddle nose deformity may occur. Laryngotracheal involvement may be life-threatening. The initial symptoms are tenderness over the larynx and trachea, hoarseness, stridor and cough, leading to upper airway obstruction as the inflammation continues. Eye involvement in RP can affect half of patients during the course of the disease. The most common lesions are scleritis, episcleritis and conjunctivitis. However, keratitis, uveitis, as well as retinal vasculitis may be seen. Despite the fact that the articular cartilage is spared, arthritis is common in RP and can manifest as an oligoarticular, non-erosive, seronegative arthritis.

15.1.4 RP Associated Disorders

Many systemic diseases are associated with RP such as vasculitis [Behçet's disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), Takayasu's arteritis (TA), leukocytoclastic vasculitis]. It is also associated with connective tissue diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), antiphospholipid syndrome (APS) etc. Other diseases associated with RP are haematological malignancies, cryoglobulinaemia, pernicious anaemia, primary biliary cirrhosis, myasthenia gravis, psoriasis, atopic dermatitis and others.

15.1.5 Pathogenesis

The aetiology of RP pathogenesis is not known but it is thought that an autoimmune mechanism is implicated. About half of patients develop antibodies to collagen type II. In addition, matrilin-1 is a cartilage matrix protein found in cartilaginous structures. Injection of this protein into mice causes a clinical picture similar to RP described in humans.

15.1.6 Diagnosis

No specific laboratory or imaging techniques are required for RP diagnosis. The diagnosis is made on clinical grounds. McAdam et colleagues proposed that the diagnosis of RP requires three or more of the following clinical criteria: (a) bilateral auricular chondritis, (b) non-erosive seronegative inflammatory polyarthritis, (c) nasal chondritis, (d) ocular inflammation, (e) cochlear or/and vestibular dysfunction, and a compatible biopsy showing inflammation of the cartilage with lymphocytic infiltration (CD4⁺) together with C3 and immunoglobulin deposition.

15.1.7 Management

If the disease is limited, non-steroidal anti-inflammatory drugs (NSAIDs) can be used. In some cases, corticosteroids (CS) may be used to combat inflammation. Other drugs commonly used are dapsone, methotrexate (MTX), azathioprine (AZA) and cyclophosphamide (CP).



Fig. 15.1 Relapsing polychondritis

RP is a multisystem inflammatory disease of unknown aetiology affecting the cartilaginous structures. All types of cartilage may be involved. Chondritis of auricular, nasal, and tracheal cartilage predominates in this disease. External ear involvement is the presenting symptom in almost all patients. RP typically attacks the cartilaginous portion of the pinna, sparing the lobe which lacks cartilage. Auricular chondritis presents with pain, redness, swelling and tenderness involving one or both ears (Fig. 15.1a, b). Ocular manifestations occur in approximately 60% of patients with RP. The most common are scleritis, episcleritis (Fig. 15.1c), keratitis and conjunctivitis, which may occur early. The differential diagnosis includes infection or other systemic vasculitides. The McAdam's criteria were the initial diagnostic criteria.

15.2 Diffuse Idiopathic Skeletal Hyperostosis (DISH)

15.2.1 Introduction

Diffuse idiopathic Skeletal Hyperostosis (DISH) also known as Forestier's disease is not a true arthropathy, since the articular cartilage, bone margins and synovium are not affected. DISH is characterized by ossification of skeletal sites subjected to stress especially tendons and ligaments.

15.2.2 Epidemiology

It is a common disorder occurring in elderly population and it is associated with obesity, hypertension, diabetes mellitus, dyslipidaemia, hyperuricaemia and other metabolic conditions. The prevalence and incidence are undetermined but it is estimated about 10–15% of the general elderly population.

15.2.3 Clinical Manifestations

DISH is often asymptomatic and its diagnosis is radiographic. Spinal stiffness is the most common complaint, whereas spinal pain is not unusually a major problem.

Extra spinal lesions have been described for most joints but the hip is often affected.

Since the disease affects mainly the spine, knowledge of the radiographic criteria allows the correct diagnosis to be made: The radiographic findings of the spine are the following:

1. Flowing ossification of at least four contiguous vertebral bodies
2. Preservation of disc spaces
3. Ossification of multiple tendinous and ligamentous sites of the appendicular skeleton
4. Normal mineralization ossification of the ligaments and soft tissues must be observed around 4 or more contiguous vertebral bodies in order to make the diagnosis of DISH.

The thickness of ossification can range from 1 to 20 mm. The ossification may be so extensive as to render the spine as immobile similar to ankylosing spondylitis (AS). The thoracic spine is the most common site of involvement. The ossification usually occurs anteriorly and/or on the right side of the lower thoracic spine. Ossification may affect the anterior part of the cervical spine. These ossifications can comprise the oesophagus, causing dysphagia and disorders of the larynx or pharynx.

Myelopathy can result from ossification of the posterior ligaments.

15.2.4 Differential Diagnosis

The main differential diagnosis is axial spondyloarthritis (AxSpa). The main features for distinguish DISH from AxSpa are the presence of ossification around the sacroiliac joint, the absence of sacroiliitis, the absence of extra-articular manifestations and the age of the patient. Symptoms of AxSpa begin at a young age, usually late adolescence and early adulthood. They consist of inflammatory spinal pain, stiffness and decreasing range of spinal motion. On the other hand, DISH affects middle-aged and elderly people and it is often asymptomatic, or is associated with mild dorsolumbar pain and some restriction of spinal mobility.

15.2.5 Treatment

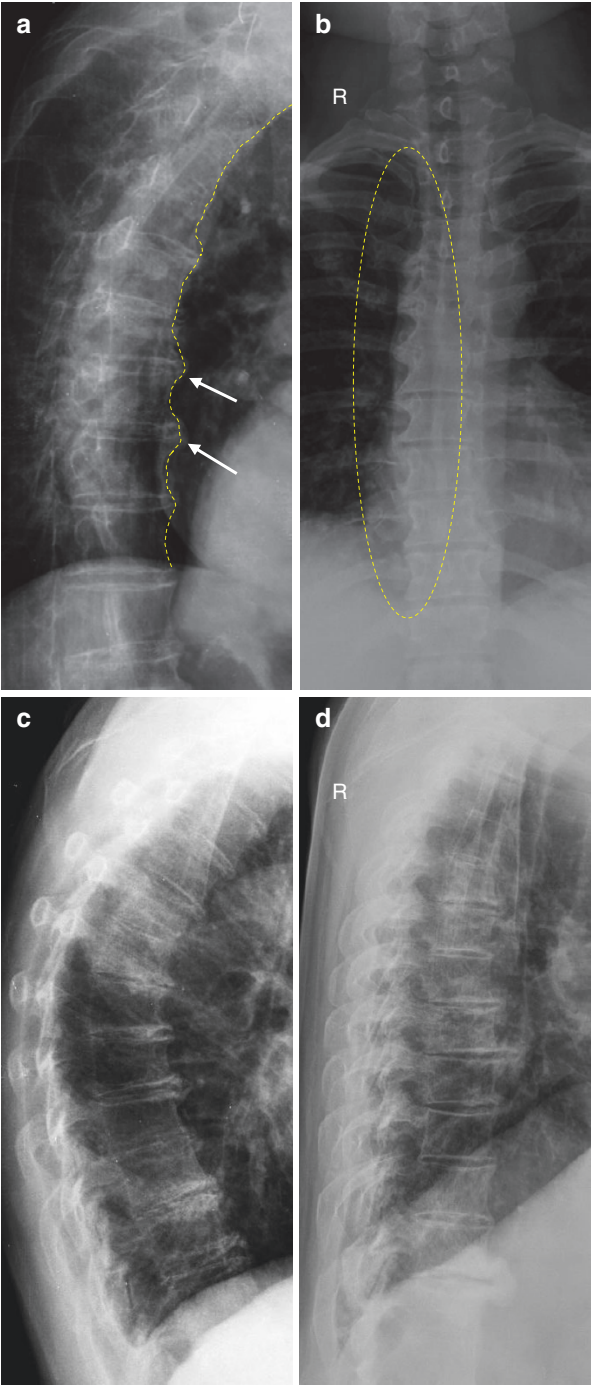
The therapeutic approach in DISH is mainly empirical and symptomatic. Analgesics, local or systemic NSAIDs, physiotherapeutic modalities and lifestyle changes are the main suggestions by the physicians.

Fig. 15.2 Diffuse idiopathic skeletal hyperostosis

DISH or Forestier's disease is a skeletal disorder, associated with stiffness and back pain, but it often it causes no signs or symptoms. It commonly affects older males. Forestier's disease is an eponym used to describe this condition, after the name of the physician who recognised it.

The aetiology of DISH is poorly understood but underlying metabolic disease is a common finding.

Figure 15.2a and b show two different patients with moderate findings (calcification of the anterior longitudinal ligament and osteophyte formation – yellow dashed line and white arrows respectively). Note the calcification and ossification which is more prominent on the right side of the spine in Fig. 15.2b (right side – «melted candle wax» appearance – yellow dashed elliptical circle). Figure 15.2c and d show two different patients with early findings of DISH.



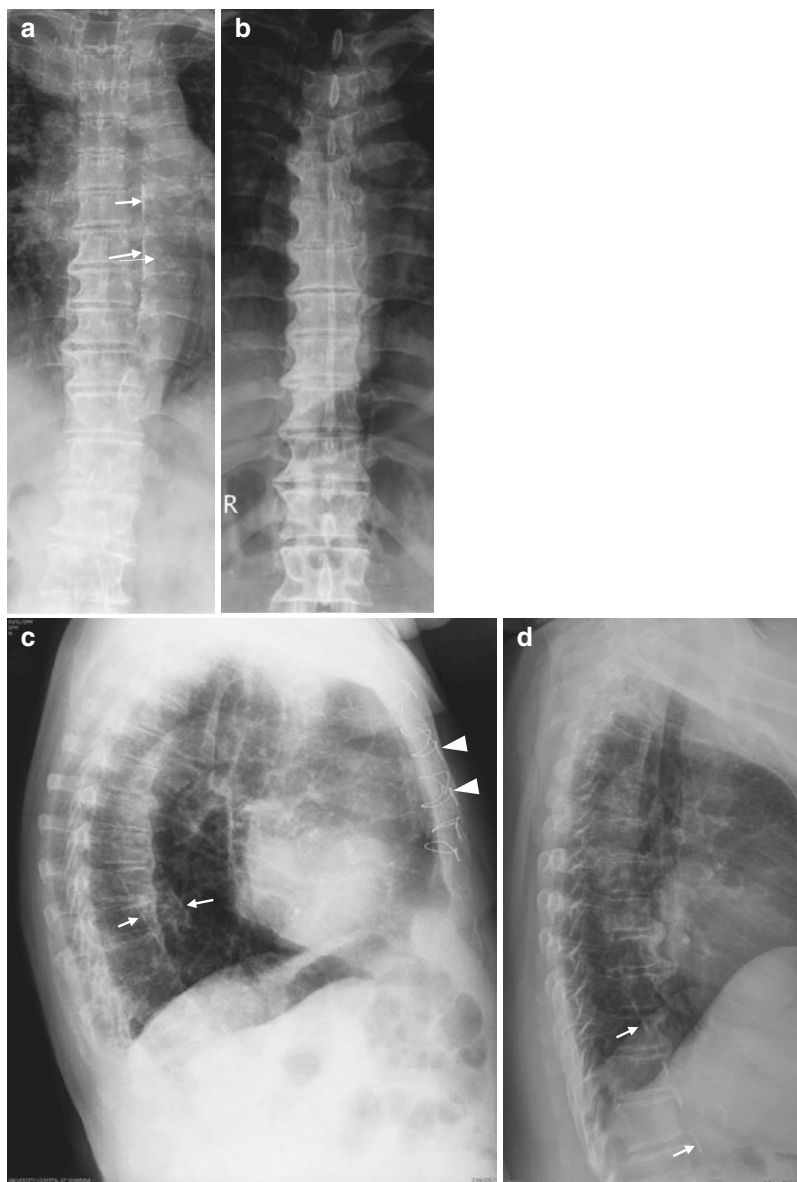


Fig. 15.3 Severe cases of diffuse idiopathic skeletal hyperostosis

Usually, DISH does not produce pain or limited range of motion (ROM) in the majority of cases. But, there are cases where the symptoms decrease the everyday quality of life in the affected population. The severity of the symptoms has been linked with the severity of the so called cardiometabolic syndrome. All of the presented radiographs are from patients suffering from diabetes mellitus, hypertension and dyslipidaemia. You can notice that except the already mentioned findings of DISH (Fig. 15.3a, b), calcification of the aorta is present (Fig. 15.3a, c, d - white arrows). In Fig. 15.3c a lateral view x-ray is shown. You notice the DISH findings affecting the thoracic spine as well as sternotomy sutures placed after cardiac surgery (white arrowheads). The patient in Figure 15.3d was complaining about dysphagia and no other apparent pathology could be found after the appropriate investigations. Thus, it was attributed to the degenerative changes of the thoracic spine.



Fig. 15.4 Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome

The SAPHO syndrome stands for Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. It was described by Chamot et al. in 1987. The exact aetiopathogenesis is not clear. There are no acceptable diagnostic criteria, although many criteria have been published so far. Diagnostic criteria proposed by Benhamou for SAPHO syndrome are: Inclusion criteria – (a) skin manifestations of severe acne, (b) skin manifestations of palmoplantar pustulosis, (c) hyperostosis with or without dermatosis, d) chronic recurrent multifocal osteomyelitis involving axial or peripheral skeleton, with or without dermatosis. Exclusion criteria – (a) septic osteomyelitis, (b) infectious chest wall arthritis, (c) infectious palmoplantar pustulosis, (d) palmoplantar keratoderma, (e) DISH, (f) osteoarticular manifestations of retinoid therapy.

The skin lesions in SAPHO syndrome are characterised on skin biopsy by infiltrations of inflammatory cells, known as neutrophilic pseudoabscesses. In Fig. 15.4a–c, a middle-aged female with a mild exacerbation of the disease and the formation of pustular lesions on hands and feet is depicted (black arrows). In Fig. 15.4d, another case with older lesions. You can notice that the pustular lesions get flat and the colour becomes dark brown until they disappear (yellow arrows). In the next figure the imagistic features are presented.

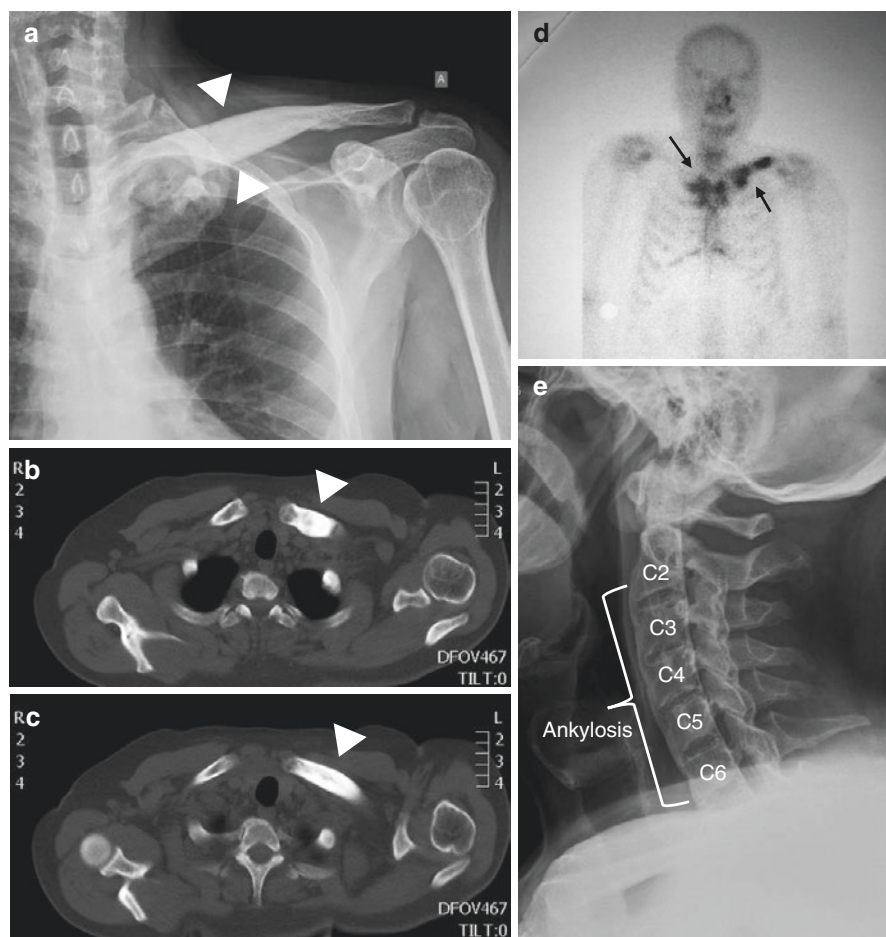


Fig. 15.5 Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome – imaging findings
Radiologic findings in SAPHO syndrome include osteitis, hyperostosis, and osteosclerosis. Hyperostosis, is highly characteristic of SAPHO, and it is characterised by chronic periosteal reaction and cortical thickening, resulting in bone hypertrophy (Fig. 15.5a – bone hypertrophy of the left clavicle on plain radiography – white arrowheads). Computed tomography (CT) is helpful in locating the lesions and providing information on adjacent soft tissues. CT cannot distinguish between SAPHO lesions, osteomyelitis and malignancy (Fig. 15.5b and c from the same patient – bone hypertrophy of the left clavicle – white arrowheads). Bone scintigraphy is important in diagnosing SAPHO syndrome, particularly for detecting early bone involvement (Fig. 15.5d – sternoclavicular joints and left clavicle involvement – black arrows). The bull-horn sign is the typical characteristic of SAPHO syndrome in bone scintigraphy images. SAPHO syndrome presents with arthro-osteitis of the upper anterior chest wall. Spinal involvement is sometimes similar to AxSpA. As you can notice, the patient in Fig. 15.9e had also cervical spine ankylosis (C2-C6) mimicking AS.

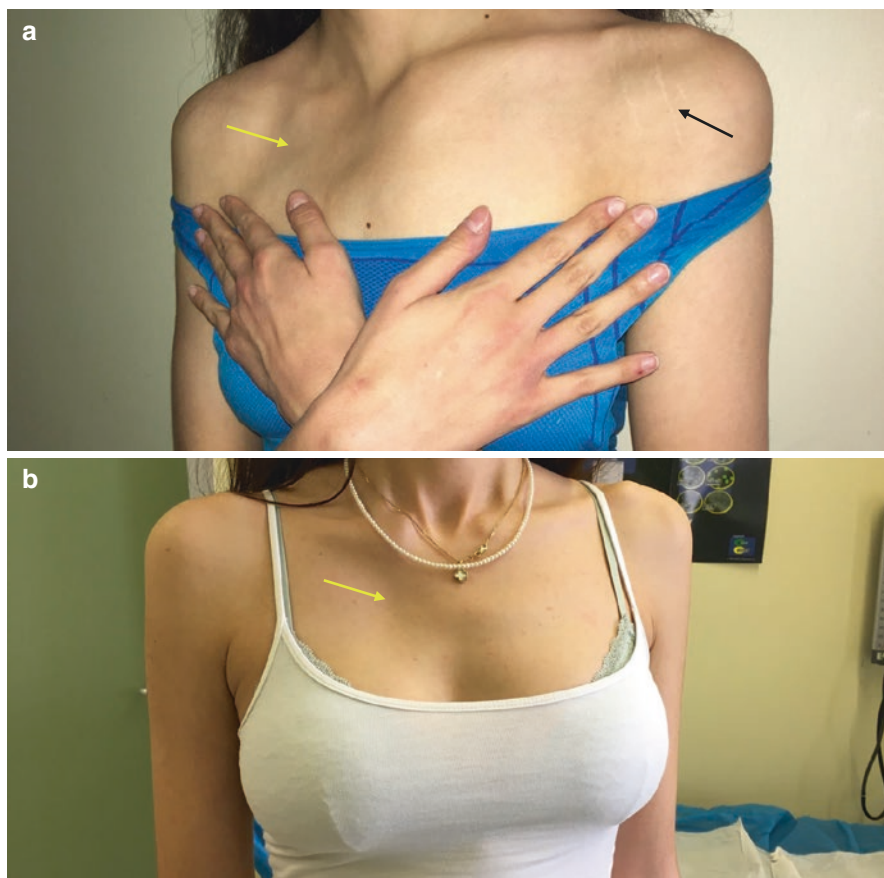


Fig. 15.6 Marfan syndrome

Marfan syndrome is a multisystem connective tissue disorder whose cardinal features affect the cardiovascular system, eyes and skeleton. It is a heritable disorder and the basic defect is in fibrillin 1, the principal constituent of extracellular matrix microfibril. Skeletal manifestations of Marfan's syndrome include excessive stature, abnormal body proportions with a long arm span and an abnormally low ratio of the upper segment to the lower segment (dolichostenomelia), elongated digits (arachnodactyly), anterior thoracic deformity (pectus excavatum, carinatum, or an asymmetric combination). The diagnosis of Marfan syndrome relies on a set of defined clinical criteria (the Ghent nosology) developed to facilitate accurate recognition of the syndrome and improve patient management and counseling. In 2010, an international panel of experts revised the criteria in order to decrease the risk of premature or missed diagnosis.

In Fig. 15.6a and b you can notice the chest asymmetry (yellow arrow), whereas in Fig. 15.6a the presence of skin striae on the left shoulder (black arrow) but also the increased length of the fingers (arachnodactyly) are shown.



Fig. 15.7 Different signs of Marfan syndrome

Figure 15.7a arachnodactyly is often a subjective finding. The condition is characterised by elongation and narrowness of the long bones, particularly those of the metacarpals, fingers and toes. Figure 15.7b the thumb sign/test (the Steinberg sign) is used for the clinical evaluation of Marfan patients. You ask the patient to fold the thumbs into the closed fist. This test is positive if the thumb tip extends from palm of hand. Figure 15.7c the wrist sign/test (the Walker-Murdoch sign) is used along the thumb sign for the evaluation of patients with Marfan syndrome. You ask the patient to grip the wrist with the opposite hand. If thumb and fifth finger of the hand overlap with each other, this represents a positive test. Figure 15.7d flexible joints (normal approx. 90°), another test for evaluation of Marfan syndrome. Figure 15.7e, f hindfoot valgus (black dashed line) in combination with lowering of the midfoot. Note the collapsed arch of the foot (black arrow) that comes in contact with the ground.



Fig. 15.8 Lichen planus

Lichen planus is a chronic inflammatory disorder of unknown origin that can affect the skin, hair, nails and mucous membranes. It is believed to result from an abnormal T-cell-mediated immune response in which basal epithelial cells are recognised as foreign because of changes in the antigenicity of their cell surface. The skin and oral mucosa are the most frequently involved areas. Cutaneous lichen planus is characterised by flat-topped red to violaceous papules that can be intensely itchy (Fig. 15.8a – black arrowheads) or even as erythematous scaly plaques (Fig. 15.8b – black arrows). The plaques are crossed by fine white lines called Wickham's striae. Koebner's phenomenon may be present (Fig. 15.8a–c – thick black arrows). Figure 15.8d depicts nail pterygium in lichen planus. This is the result of an irreversible damage to the nail matrix. In Fig. 15.8e, including the insert figure, the oral mucosa lesions are bilateral and are associated with a network of white-lined plaques (yellow arrowheads) and erosive lesions (green arrowheads).

Histologic examination of skin or mucosal biopsy specimens is useful to confirm the diagnosis.



Fig. 15.9 Pachydermoperiostosis

Pachydermoperiostosis is a hypertrophic osteoarthropathy. It is a rare hereditary disorder characterised by digital clubbing, pachydermia (face and scalp) and periostosis associated with pain, polyarthrititis, cutis verticis gyrata, seborrheic dermatitis, eyelid ptosis, and hyperhidrosis. This patient visited the outpatient clinic due to pain on both hands and knees. In Fig. 15.9a you can notice the coarsening of the facial features with furrowing of the forehead skin (pachydermia) and mild manifestations of facial acne. Bilateral blepharoptosis is also evident with thickening of the eyelids. Figure 15.9b and c show enlargement of the fingers with digital clubbing. In Fig. 15.9d, seborrheic dermatitis of the chest is evident. The left knee was swollen and was tender on palpation with restricted ROM (Fig. 15.9e).

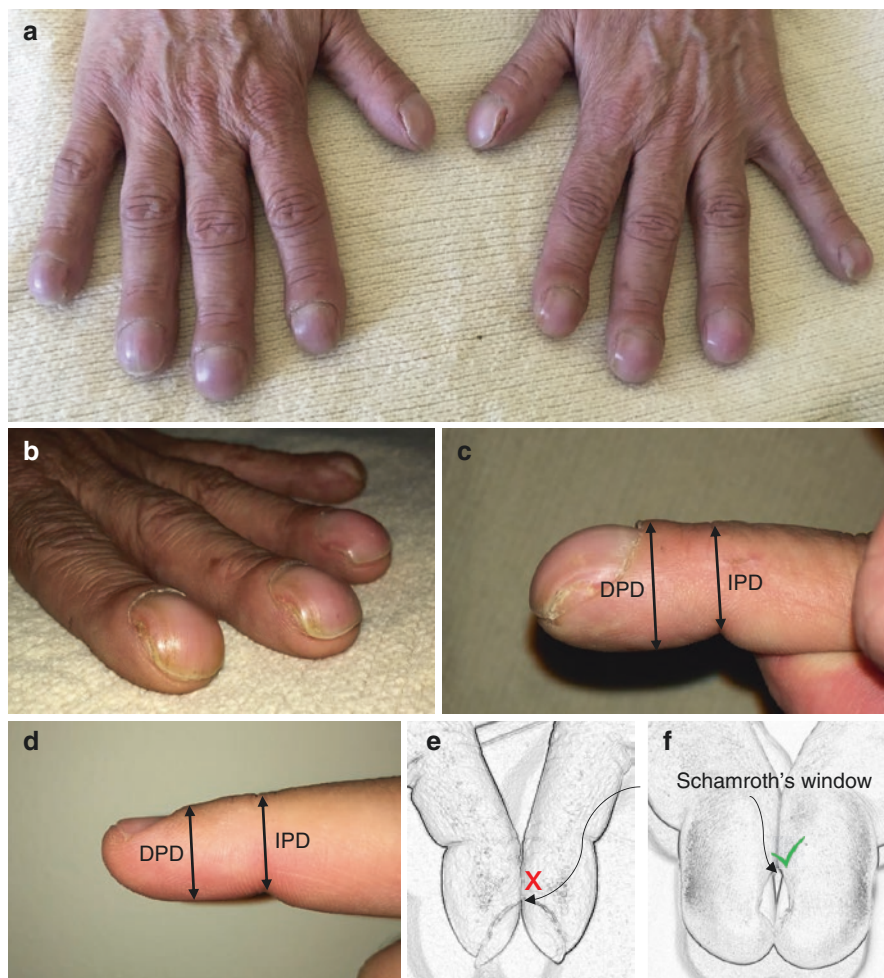


Fig. 15.10 Digital clubbing/Hippocratic fingers

Digital clubbing was first described by Hippocrates nearly 25 centuries ago and is regarded to be the oldest sign in clinical medicine. Although clubbed fingers are mostly asymptomatic, it often reflects the presence of dreadful internal illness like lung cancer, idiopathic pulmonary fibrosis, or underlying suppurative conditions (Fig. 15.10a, b). In musculoskeletal diseases, pachydermoperiostosis, a rare hereditary disorder, is characterised by digital clubbing among other manifestations (see Fig. 15.9). In Fig. 15.10c, a clubbed finger has an altered phalangeal depth ratio in comparison with a normal one (Fig. 15.10d). The interphalangeal depth (IPD) is less than the distal phalangeal depth (DPD) whereas in normal subjects the IPD is approximately equal to the DPD. Schamroth's sign is an easy to use clinical indicator for early stages. In normal individuals a distinct aperture (Schamroth's window) which is usually diamond-shaped, is formed at the base of the nail bed when two fingers held together with nails facing each other. Early clubbing obliterates this window (Fig. 15.10e, f).



Fig. 15.11 Dupuytren's contracture

Dupuytren's contracture or Dupuytren's disease is a benign proliferative disorder characterised by fascial nodules and contractures of the hand. It is more prevalent in males (2:1 male to female ratio) and usually it develops between the fifth and seventh decade of life. It has been associated with trauma, alcoholism, diabetes, human immunodeficiency virus (HIV) and antiepileptic medications. Patients are complaining about the presence of painful nodules or a cord-like formation under their skin with decreased ROM of the affected finger. It can be unilateral or bilateral and the most frequent affected finger is the 4th (ring finger) with the small, middle and index fingers to be affected in decreasing frequency. In Fig. 15.11a, the 5th finger of the left hand and the 4th finger of the right hand are affected with severe flexion of both. Figure 15.11b shows a patient with Dupuytren's contracture of the index finger which is not so common. In Fig. 15.11c a mild deformity is seen. Non-operative treatments can be applied with ROM exercises and injection of *Clostridium histolyticum* collagenase but also a surgical resection/fasciectomy may improve the contracture (Fig. 15.11d). Recurrence can be as high as 30–40% especially when non-operative measures are applied.



Fig. 15.12 Garrod's pads

Garrod's pads or Garrod's disease is an ectopic manifestation of Dupuytren's disease. It is characterised by calluses on the dorsal aspect of the interphalangeal (IP) joints. In Fig. 15.12a (insert figures in more detail) Dupuytren's contracture is seen bilaterally whereas in Fig. 15.12b and c the Garrod's pads are visible (black arrows).



Fig. 15.13 Carpal tunnel syndrome

The most prevalent aetiology of thenar eminence atrophy is carpal tunnel syndrome (CTS). Three muscles are considered part of the thenar eminence: abductor pollicis brevis, flexor pollicis brevis, and opponens pollicis which are innervated by the median nerve (MN) (except the deep head of the pollicis brevis – ulnar nerve). In CTS the MN is compressed. Pain, numbness, and tingling in the thumb, index finger, middle finger, and the thumb side of the ring finger are the typical symptoms. Later, weak grip strength may occur and after a long period of time, the muscles at the base of the thumb may waste away (black arrows). It can be unilateral (Fig. 15.13a, b) but in about 50% of the cases both sides are affected (Fig. 15.13c). Musculoskeletal ultrasound (MSUS) can help in diagnosis of CTS. Enlargement of the nerve seems to be the most sensitive and specific criterion, but the cut-off value is still a matter of debate. The normal cross-sectional area is given at 9–11 mm². Figure 15.13d shows a normal MN (8 mm²) whereas Fig. 15.13e shows an enlarged nerve (15 mm²) (white arrowheads). Electrophysiological studies are also used for its diagnosis.



Fig. 15.14 Vitiligo and liver spots (age spots)

Vitiligo is an acquired pigmentary disorder (Fig. 15.14a). Several overlapping pathogenetic mechanisms are implicated leading to loss of functional melanocytes and loss of the “normal” colour of the affected skin. Immune-mediated and toxin-associated damage to melanocytes are the most probable pathological mechanisms. On the other hand, liver or age spots (Fig. 15.14b) appear with age progression and are small dark areas of the skin. They usually appear in adults older than 50 in sun-exposed areas particularly the hands, face, shoulders, arms and forehead, and should be differentiated from vitiligo.



Fig. 15.15 Algodystrophy

Algodystrophy is also known as complex regional pain syndrome (CRPS). In 1864, it was presented in detail for the first time by Mitchell et al. They gave the term “causalgia” which means “burning pain”. The initial observation was made after peripheral traumatic nerve injury due to distal extremity gunshot wounds in soldiers injured in the American civil war. The exact cause is unknown but it can be classified as CRPS-I and CRPS-II. CRPS-I affects individuals without a confirmed nerve injury. CRPS-II is diagnosed in patients that have suffered an associated nerve injury. Other types of injuries that could lead to algodystrophy include sprains and strains, surgeries, fractures, contusions, crush injuries and stroke. The onset is mostly associated with trauma, immobilisation, injections, or surgery. Patients are complaining of a persistent severe pain and they usually describe it as a burning sensation to the affected region or a pins and needles sensation. Pain is associated with abnormal cutaneous sensitivity manifesting as allodynia (where an innocuous stimulus such as touch induces pain) and hyperalgesia (where pain perception is increased to a given painful stimulus, such as a pinprick). Swelling of the involved area is common and often associated with reticular or livedoid appearance over the skin of the affected limb. Alteration in peripheral sympathetic tone may lead to other changes in skin colour which become cyanotic, pale or red. Currently, the Budapest diagnostic criteria can be applied in order to diagnose patients with this disorder. Nevertheless, the diagnosis of CRPS is based solely on clinical signs and symptoms. There are no specific diagnostic procedures to confirm the clinical diagnosis. Plain radiography is the first exam performed and may show bone demineralisation, but it is positive only in chronic stages. Magnetic resonance imaging (MRI) shows more clear-cut abnormalities with regional or diffuse bone loss. Three-phase ^{99m}Tc Technetium bone scans are abnormal in about 75% of the cases. In Fig. 15.15a there is marked swelling of the depicted hand. In Fig. 15.15b there is marked swelling of the right hand. In Fig. 15.15c you can notice the difference between the affected and the contralateral upper limb.

Treatment consists of the combination of bisphosphonates, calcium supplements, hyperbaric oxygen therapy, physiotherapy, and partial weight bearing over the affected limb.



Fig. 15.16 Remitting seronegative symmetrical synovitis with pitting oedema syndrome

The RS3PE syndrome stands for Remitting Seronegative Symmetrical Synovitis with Pitting Edema. RS3PE was first described in 1985 as a subset of acute-onset polyarthritis. The main characteristics of RS3PE include symmetrical synovitis, pitting oedema on the dorsal side of the hands, lack of rheumatoid factor (RF), and response to a short course of CS. As it is a rare disorder it is often overlooked by the clinicians.

In Fig. 15.16a, one can notice the marked swelling on the dorsal aspect of both hands. In Fig. 15.16b, a + 3 pitting oedema is seen (black arrowheads).

Treatment consists of relatively small doses of prednisolone (5–20 mg), NSAIDs and hydroxychloroquine (HCQ) may provide an added advantage. Some cases have been treated with immunosuppressive drugs. Remission is usually achieved. If not, a patient with RS3PE may have an underlying malignancy and must be treated appropriately.



Fig. 15.17 Adult-onset Still's disease

Adult-onset Still's disease (AOSD) is characterised by the classic triad of persistent high spiking fever, arthralgia, and salmon coloured skin rash. It was named after an English physician, George Still.

Due to absence of characteristic serological biomarkers and the presence of several nonspecific symptoms, AOSD is often difficult diagnosed. Thus, it is typically considered as a diagnosis of exclusion. Nevertheless, a definitive diagnosis should be made in grounds of the Yamaguchi or Fautrel criteria which comprise as major criteria high spiking fever, polyarthritis, sore throat and evanescent truncal skin rash. It is important though to exclude infectious, malignant, and other connective tissue diseases. In 60–80% of AOSD cases, a macular or maculopapular evanescent salmon-pink skin rash appears together with the fever spikes. It is predominantly found on the proximal limbs and trunk. The joints usually implicated are the wrists but any joint can be affected. Most of the patients develop persistent chronic arthritis even when systemic symptoms have stopped. First-line treatment for AOSD are CS. MTX can be used as a sparing agent. In refractory cases (polycyclic course) in case of systemic AOSD, interleukin (IL)-1 inhibitors have been proved efficient whereas in the articular AOSD cases, IL-6 inhibitors or tumour necrosis alpha (TNF- α) inhibitors can be used.

In Fig. 15.17, a patient with high spiking fever, arthralgias mainly on the wrist, metacarpophalangeal joints (MCPs) and proximal interphalangeal joints (PIPs), leukocytosis with neutrophilia, thrombocytosis and increased ferritin levels (13.450 ng/ml) developed this evanescent salmon-coloured skin rash.

Fig. 15.18

Dermographism in AOSD

There are many case reports in the literature supporting that patients suffering from AOSD may develop concomitant urticarial and dermographic lesions, as in this patient in Fig. 15.18.

These patients respond well to CS and antihistamines.





Fig. 15.19 IgG4-related disease

Immunoglobulin G4-related disease (IgG4-RD) represents an immune-mediated fibroinflammatory condition that can affect various organs and tissues. Patients often present with the development of a mass in the affected organ or diffuse enlargement of an organ. It generally occurs most commonly in middle-aged and older men. The pathogenesis of the disease is not fully elucidated as findings are consistent with autoimmune but also allergic disorders. It is characterised by infiltration with lymphocytes and IgG4-rich plasma cells as well as storiform fibrosis.

This is a patient with IgG4 related ophthalmic disease that had orbital manifestations. Clinically, a periorbital oedema with a degree of exophthalmos is seen bilaterally. Also, the patient manifested IgG4-related sialadenitis and cervical lymphadenopathy (Fig. 15.19a). An MRI of the head revealed a mass lesion around the optic discs and enlarged salivary glands. Finally, laboratory and histopathology results confirmed the diagnosis. Figure 15.19b shows the same patient after treatment with corticosteroids (CS). You may notice the disappearance of periorbital oedema and exophthalmos.

IgG4-RD is a rare entity and, in such patients, a differential diagnosis for malignancy should be ruled out.

Fig. 15.20 Paget's disease – leg bowing
Osteitis deformans or Paget's disease represents a bone disease with an imbalance of bone formation and resorption. At the beginning, osteolysis is accompanied by some level of repair. It may occur in one or more bones (monostotic and polyostotic Paget's disease respectively). It occurs rarely before the age of 20 with most patients being affected after the age of 50. Saber tibia or saber shin is a malformation of the tibial bone resulting in leg bowing due to Paget's disease. Figure 15.20 shows a 63-year old patient with the characteristic saber tibia due to Paget's disease. The treatment consisted of bisphosphonates and analgesics.



Fig. 15.21 Osteitis condensans ilii

Osteitis condensans ilii (OCI) is characterised by benign sclerosis of the ilium adjacent to the sacroiliac joint. Typically, it is found bilaterally and has a triangular shape. Usually, OCI is not symptomatic, but it can become symptomatic with complain of a lumbo-pelvic pain. Its prevalence has been estimated to be between 1% and 3%. No clear aetiology has been identified. The most acceptable theory is the mechanical strain affecting the auricular portion of the ilium that causes premature arthritis. It is often seen in multiparae women but nulliparous women or even men can be affected. In this figure, a female patient presented to the outpatient clinic complaining about pain and stiffness mainly on the left lumbo-pelvic region. There is marked sclerosis bilaterally, but more prominent on the left side. Treatment is usually symptomatic. Exercise should also be considered.



Fig. 15.22 Lyme disease - erythema migrans

Lyme disease (LD) is classified as a zoonosis. It is transmitted to humans from a natural reservoir among small mammals and birds by ticks. LD is caused by spirochetal bacteria from the genus *Borrelia*. The diagnosis is based on history and physical examination (history of possible exposure to infected ticks) but serological blood tests can confirm the diagnosis. The erythema migrans of LD is a red expanding patch of skin which usually starts as a red papule or macule at the site of the tick bite and gradually expands. The most typical finding is the so-called bull's eye rash. That is because a central spot surrounded by clear skin ringed by an expanding red rash is formed. Figure 15.22 depicts the erythema migrans of LD in a 39-year-old female patient, 5 days after removing a tick from the upper medial thigh (note the bite – black arrow). The patient developed mild arthralgias and low-grade fever. She has been treated successfully with a course of antibiotics.

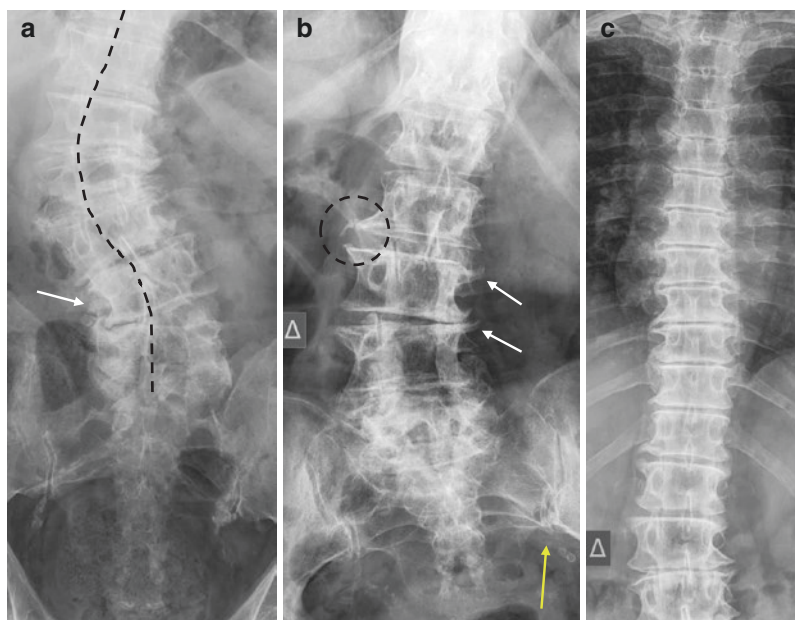


Fig. 15.23 Scoliosis of the vertebral spine

Scoliosis is a three-dimensional deformity of the spine and rib cage. It may develop as a single primary curve (Fig. 15.23a, b) or as two curves (Fig. 15.23c). In Fig. 15.23a and b, severe degenerative scoliosis of the lumbar spine is present with compensating osteophyte formation (white arrows) and sclerosis of the vertebral bones. Note the fractured osteophyte on L2 (black dashed circle). There is also narrowing of multiple intervertebral spaces. In Fig. 15.23b sclerosis of the SI joints is present due to mechanical load (yellow arrow). Figure 15.23d shows a young patient with no apparent findings other than scoliosis.

Fig. 15.23 (continued)**Fig. 15.24** Kyphoscoliosis

Kyphoscoliosis is the combination of kyphosis and scoliosis. Patients have an abnormal anteroposterior curvature of the spine and a lateral deviation of the vertebral column. It may be congenital or acquired. Due to significant anatomical changes of the rib cage, it can lead to respiratory insufficiency due to restrictive lung disease and neurological deficits due to spinal cord compression. In the above figures, note the asymmetry of the shoulders and the anatomic changes of the rib cage. Scoliosis is best seen in Fig. 15.24a and b whereas kyphotic changes are best seen in Fig. 15.24c and d. In Fig. 15.24e a CT shows the rib cage in a rotated fashion. The yellow dotted lines show where the vertebral body should be.

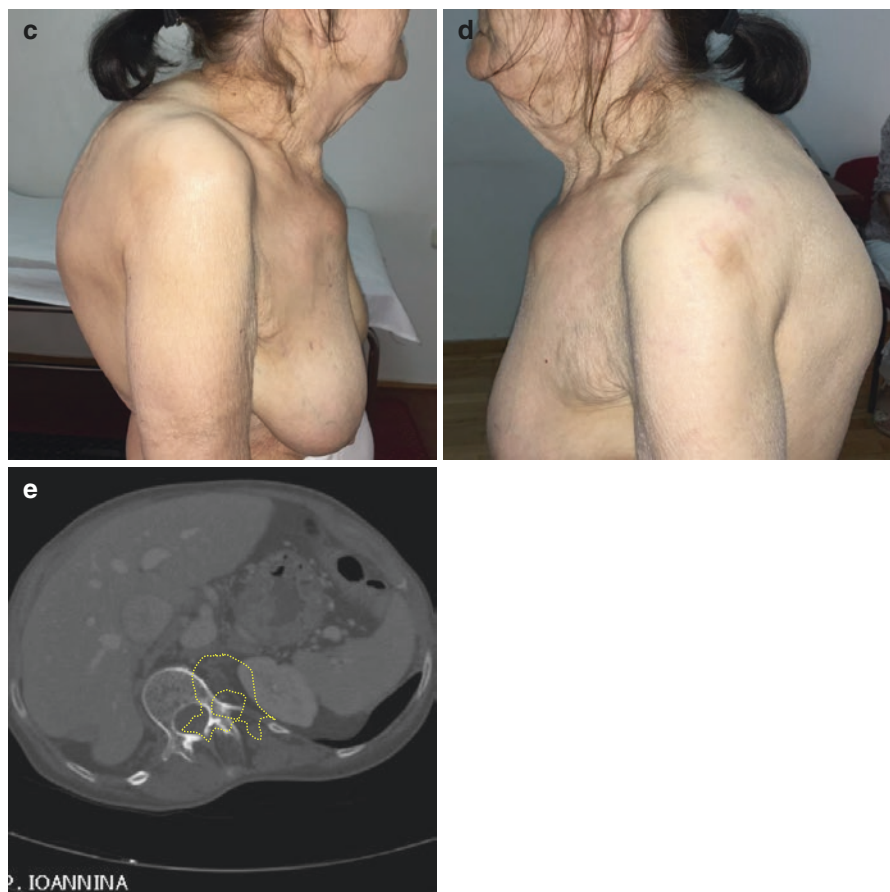


Fig. 15.24 (continued)

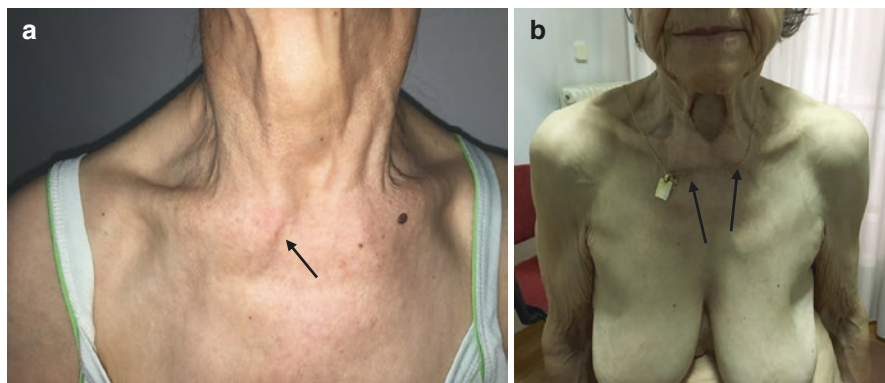


Fig. 15.25 Sternocostoclavicular joint swelling

Sternocostoclavicular joint (SCCJ) swelling (black arrows) is an underdiagnosed, albeit important entity in clinical practice. Patients usually are in pain with slightly limited ROM of the upper limb(s). Most of the times, the aetiology is a benign trauma. Common causes of SCCJ swelling include degenerative osteoarthritis (OA), septic arthritis, RA, crystal deposition disorders, metastatic disease and post-operative involvement after surgery on the neck. Sternocostoclavicular hyperostosis (SCCH) is another cause but it is a chronic inflammatory disorder which presents with erythema, swelling, and marked pain of the SCCJ. SCCJ may be unilateral (Fig. 15.25a) or bilateral (Fig. 15.25b).

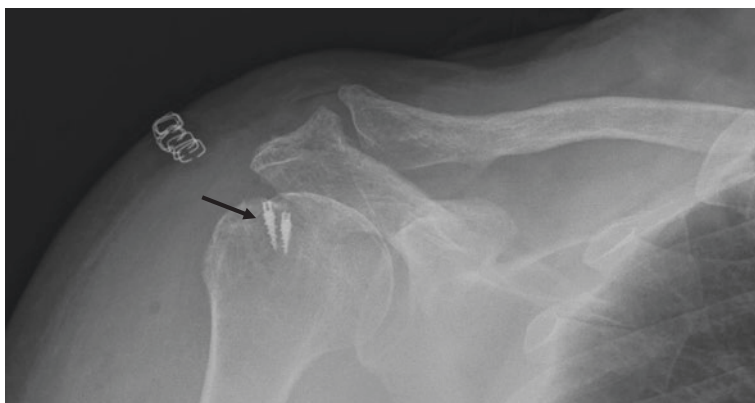


Fig. 15.26 Rotator cuff tear

Rotator cuff muscles are responsible for the stability and function of the shoulder joint. This is a group of four muscles that form a “cuff” over the head of the humerus (supraspinatus, infraspinatus, subscapularis and teres minor). The supraspinatus tear is common and can be partial or full thickness tear. This is a shoulder x-ray showing anchors in bone for rotator cuff repair after a full thickness tear of the supraspinatus (black arrow)

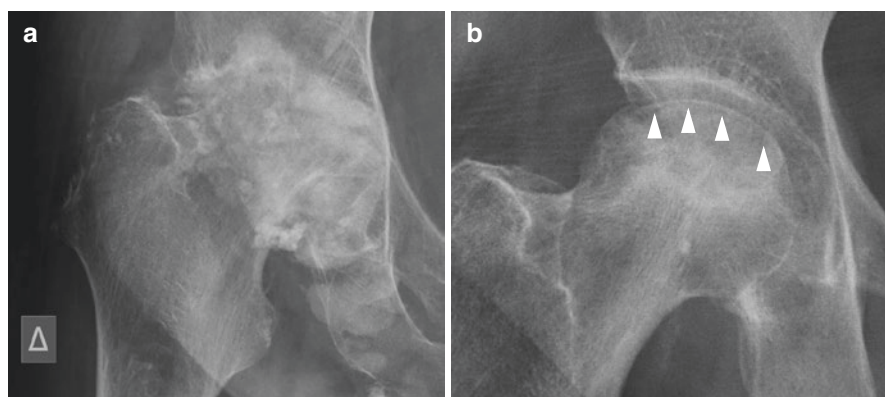


Fig. 15.27 Osteonecrosis radiographic images

Osteonecrosis (ON) or avascular necrosis refers to the final result of a number of different pathways leading to bone death and finally to bone destruction. The pain of the involved area is usually intermittent and of gradual onset, but later may advance to rest pain. The most accurate imaging modality is the MRI as plain radiographs are normal at disease onset. Figure 15.27a shows a patient with a complete collapse of the femoral head and extensive degenerative changes affecting the hip. In Fig. 15.27b the “crescent sign” is visible (white arrowheads). It is diagnostic of advanced osteonecrosis with subarticular fracture but not articular collapse.

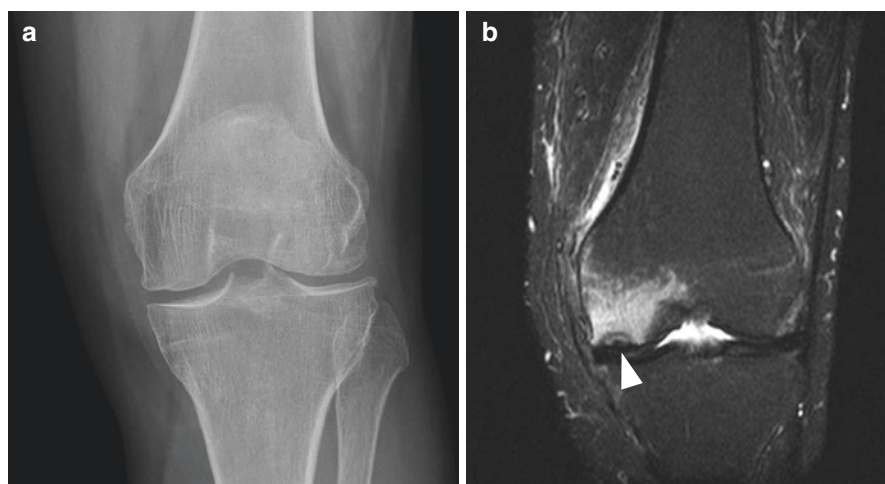


Fig. 15.28 Osteonecrosis plain radiography vs magnetic resonance imaging

As described in the above figures, plain radiographs are normal at disease onset. In Fig. 15.28a, a plain radiograph of the left knee shows on the external surface of the medial femoral condyle a small subchondral area of mild flattening with sclerosis which can be distinguished only by an experienced clinician. MRI shows the knee of the same patient on a T2-weighted FATSAT coronal view which reveals a high signal hemispheric lesion that is associated with a low signal ring (osteonecrosis – white arrowhead) and is surrounded by extensive bone oedema (Fig. 15.28b).

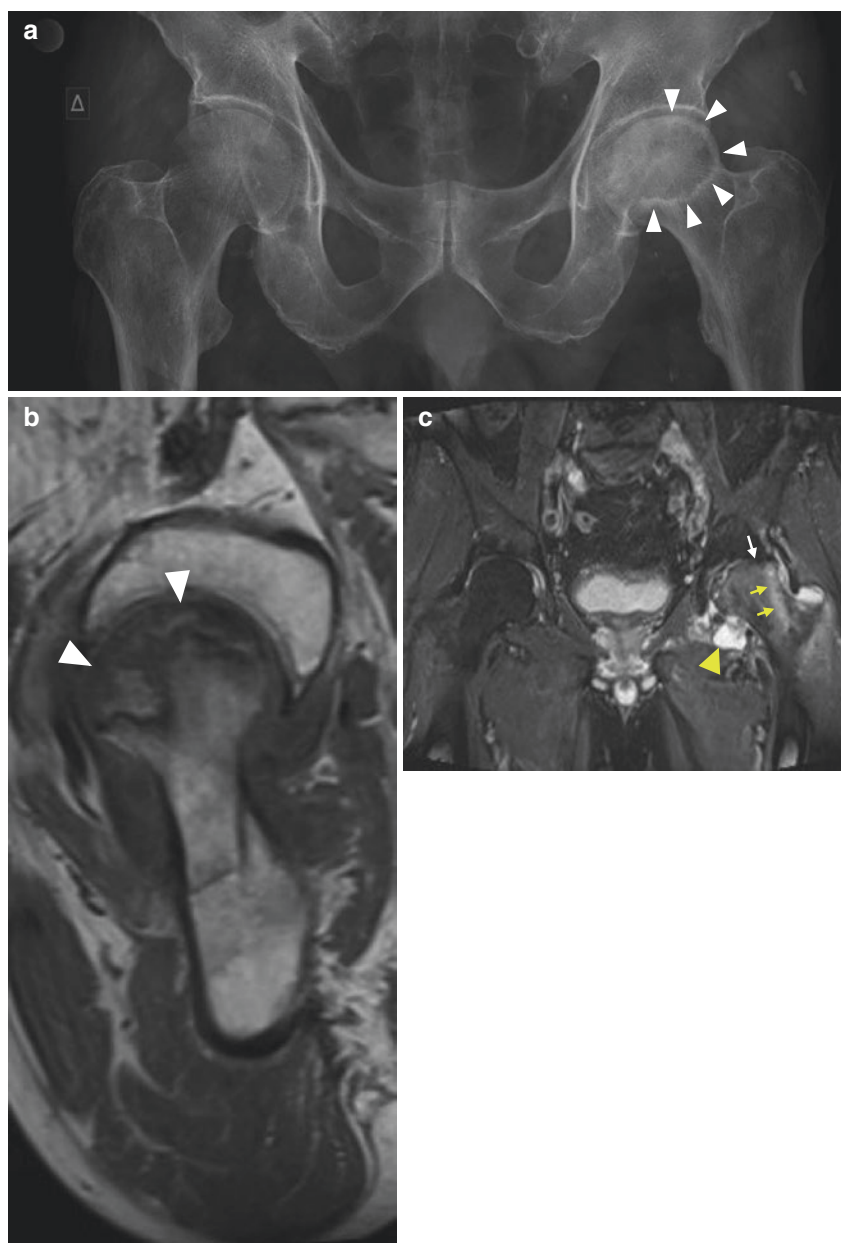


Fig. 15.29 Osteonecrosis of the left hip

Figure 15.29a Conventional radiography shows mild flattening of the left femoral head, which has an abnormal and sclerotic joint surface. Presence of osteonecrosis associated with a sclerotic ring (white arrowheads).

Figure 15.29b MRI of the left hip - T1-weighted sequences in sagittal plane reveals the osteonecrosis site in the left femoral head, which is associated with a low signal ring (white arrowheads).

Figure 15.29c MRI of the left hip - T2-weighted FATSAT coronal view reveals a flattening of the femoral head. Osteonecrosis is associated with a high signal ring (white arrow), bone marrow oedema in the head and neck (yellow arrows) as well as increased amount of fluid in the joint (yellow arrowhead).

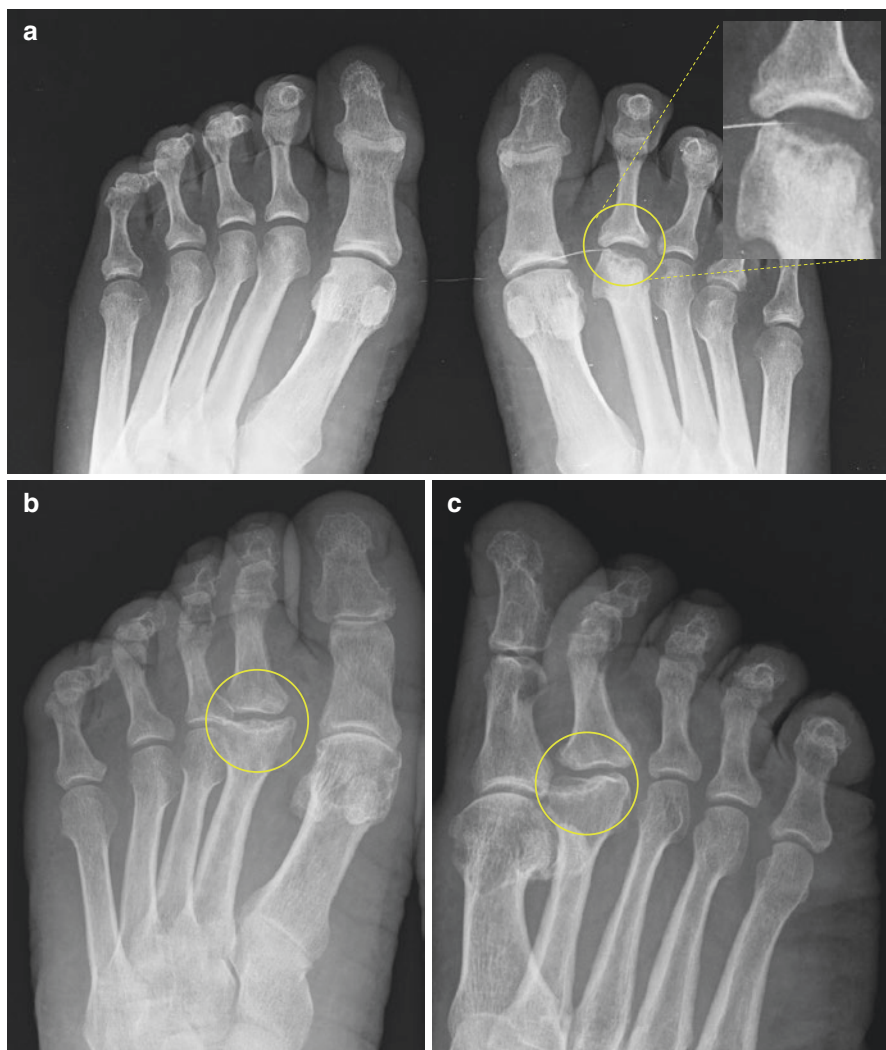


Fig. 15.30 Freiberg disease

Freiberg disease is osteochondrosis in the metatarsal bone of the foot with collapse of the articular surface. It is also known as Freiberg infraction. There is no consensus regarding the aetiology but repeated trauma or vascular insult are the most prevalent theories. The radiographic changes are consistent with avascular necrosis and this is the reason that some authors correlate it with an injury to the vascular supply to the metatarsal head. Frequently it develops in the second metatarsal head, but it may occur in any metatarsal. It can be bilateral in up to 10% of cases. Figure 15.30a–c show plain radiographs of two different patients with Freiberg’s disease of the second metatarsal heads (yellow circles). Pain is the main characteristic but most of the times it is asymptomatic.



Fig. 15.31 Arthritis-like cases

An oedematous joint does not always equals arthritis. Usually, the five signs of inflammation must be present as defined by Galen: tumor, rubor, calor, dolor and functio laesa. In Fig. 15.31a–c, the oedema seen in the external malleoli is just fat deposition which is non-tender and soft on palpation. When bilateral, it must always be investigated for Löfgren's syndrome, an acute form of sarcoidosis. In Fig. 15.31d a patient with vein insufficiency presented with a unilateral oedema of the ankle joint. Note the skin above the oedematous right ankle.



Fig. 15.32 Structural changes of the foot: pes cavus vs pes planus

The arch of the foot serves as an adaptable, supportive base for the body. Deviations in the normal structure of the foot affects the normal biomechanics of the lower limb producing disorders on weight bearing and normal gait. Pain is another manifestation of these disorders which sometimes may affect also other joints, most commonly the knees and hips.

Pes cavus or high-arch foot is the condition where there is marked accentuation of the longitudinal arch of the foot (Fig. 15.32a). This type of foot usually has decreased flexibility which limits its natural shock absorbing abilities. It can also lead to metatarsalgia, Achilles tendinitis, knee and hip pain. Pes planus or flat foot is the condition where the longitudinal arch of the foot lies flat on the ground (Fig. 15.32b, c). This type of foot is usually a hereditary condition but it can develop to many other pathologic conditions, especially inflammatory or traumatic.

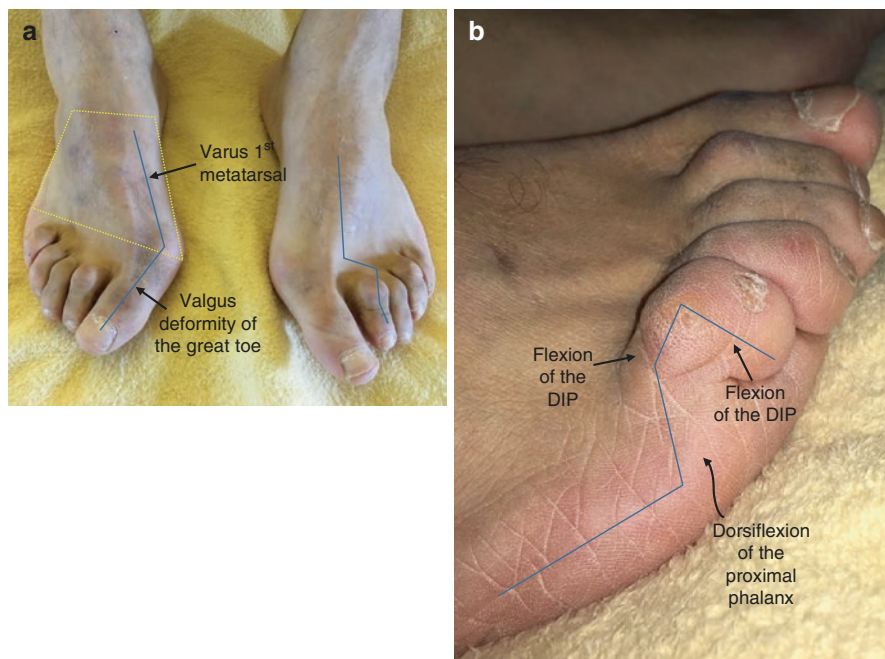


Fig. 15.33 Splay foot

Splay feet are one of the most common foot deformities. The forefoot widens in relation to the heel and certain parts of the foot do not carry weight. As a result, pain and calluses appear as well as other foot and toe deformities. Clinically, the splay foot is characterised by valgus of the great toe with or without bunion formation in association with a relative varus position of the 1st metatarsal. On the distal base of the 5th metatarsal a bunionette or the so called “Tailor’s bun-ion” may be formed because of the enlargement of the lateral aspect of the 5th metatarsal head. The deformity is located at the dorsolateral or lateral aspect of the 5th metatarsophalangeal (MTP) joint. Other toe deformities such as hammer toes or claw toes may be evident. Hammer or contracted toes are the result of a deformity of the proximal interphalangeal (PIP) joint of the 2nd, 3rd and/or toe causing a permanent bent, whereas a claw toe is another similar condition, with dorsiflexion of the proximal phalanx combined with flexion of both the proximal and distal interphalangeal joints.

In Fig. 15.33a, the widening of the forefoot in comparison with the midfoot is evident (yellow dotted asymmetric rectangle). Note also that the 1st metatarsal has a varus position and the great toe is in valgus position. Hammer toe deformity is more evident on both 2nd toes, but the 3rd and 4th are also affected (blue line).

In Fig. 15.33b, note that the 2nd – 5th toes do not carry weight anymore due to anatomical changes of the foot. The 5th toe is also characterised by the so called “claw toe” deformity.



Fig. 15.34 Crossover toes

A crossover toe describes a condition where a toe (or more than one) drifts towards another toe. The second toe is the most common affected. Hallux valgus is by far the commonest aetiology of this condition (such as those presented in Fig. 15.34a, b). Occasionally, the third toe is also implicated. It is not a specific sign. Usually, it is more prevalent in OA and RA patients

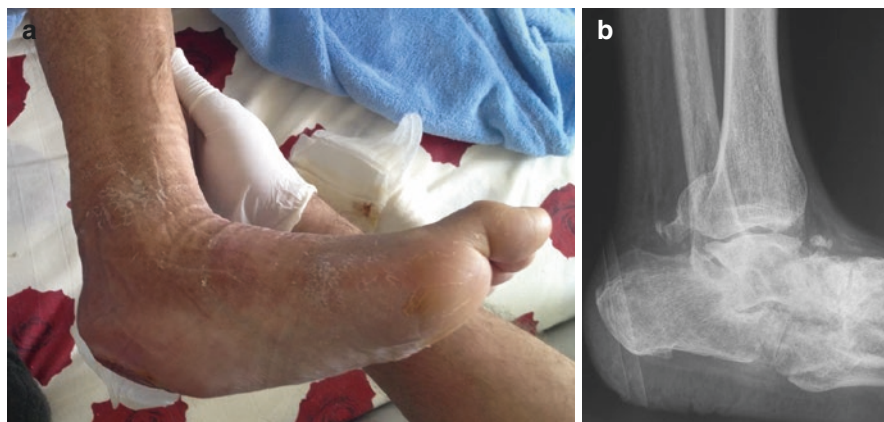


Fig. 15.35 Charcot arthropathy of the foot and ankle

Charcot arthropathy of the foot and ankle is more prevalent among patients with diabetes mellitus, but it may be associated with other peripheral neuropathies. It is well documented that RA is correlated with peripheral neuropathy and the development of Charcot arthropathy and there is a growing evidence in the international bibliography towards this direction. Furthermore, a newly-recognised subset of psoriatic arthritis (PsA) is the Charcot-like arthropathy. Charcot arthropathy is a progressive degenerative joint disorder that leads to destructive changes of the foot and ankle. Nerve damage that causes a loss of sensation is the aetiologic factor that predisposes to these destructive bone lesions. Loss of sensation increases the risk of injury to the feet and when repeatedly injured, especially the weight-bearing joints, start breaking down. In Fig. 15.35a and b a clinical and a radiological image respectively, show the complete disorganisation of the ankle joint

Fig. 15.36 Congenital C3–5 fusion

This is a lateral cervical spine x-ray showing fusion of the C3–C5 vertebral bodies, facet joints and spinous processes (white arrowheads). Note that the disc space is absent between the vertebrae, distinguishing it from postoperative or degenerative fusion. It must also be differentiated from chronic treatment-resistant cases, when synovial-based disease can lead to joint space narrowing, both cartilaginous and bony erosions, eventually leading to ankylosis. The patient was complaining of neck pain and stiffness as well as decreased ROM of the cervical spine.

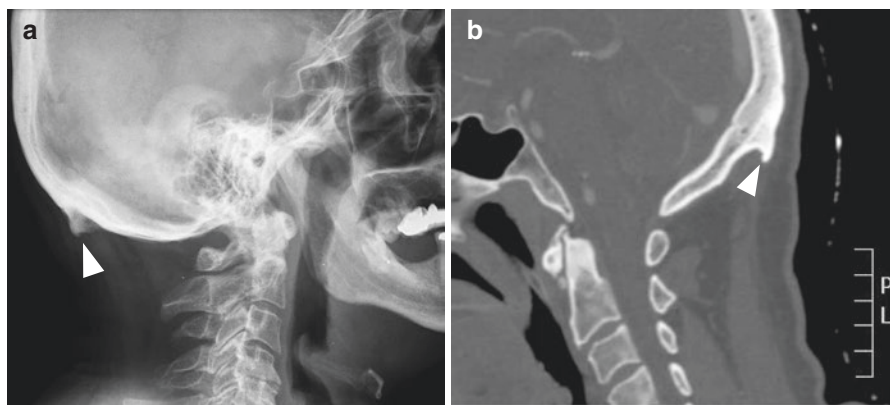


Fig. 15.37 Occipital spurs

Occipital spurs or inion hook is an exaggerated external occipital protuberance. In anthropological literature is considered as a Neanderthal trait and some authors in medical literature support that this is a normal variant. In clinical practice, patients with this kind of hyperostosis are symptomatic and complain of a tender bony swelling at the back of the neck causing pain, especially while lying down. A minority of patients complain also about headaches associated with their exaggerated external occipital protuberance. Figure 15.37a and b, a plain radiograph and a CT respectively, show two different patients with occipital spurs. Both were complaining about localised pain when lying down or when pressing this specific area with their fingers. Note that both occipital protuberances of the presented cases have a hook-like appearance (white arrowheads).

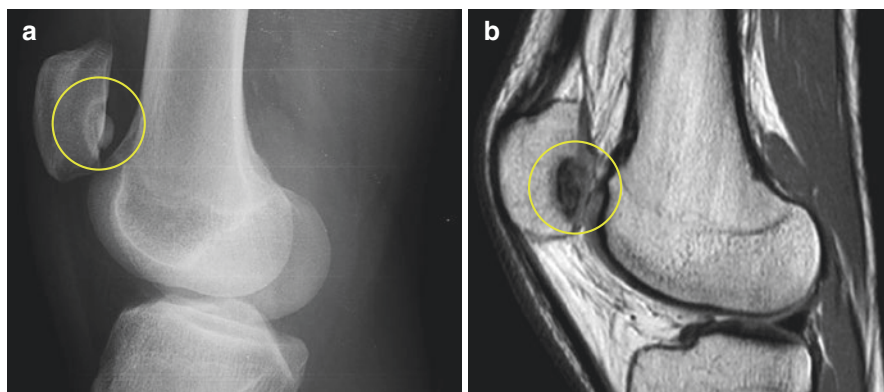


Fig. 15.38 Osteochondritis dissecans

Osteochondritis dissecans (OCD) is a pathological process affecting the subchondral bone. It may lead to secondary effects on joint cartilage, such as pain, oedema, possible formation of free bodies and mechanical symptoms, including joint locking. Figure 15.38a and b, are from a patient, 18-years old, with knee pain. OCD of the patella is rare (5%) and occurs predominantly in males. The lesion is best observed in lateral radiographic views (Fig. 15.38a – yellow circle). CT and MRI (Fig. 15.38b – yellow circle) are important for defining the location, extent and viability of the lesion.

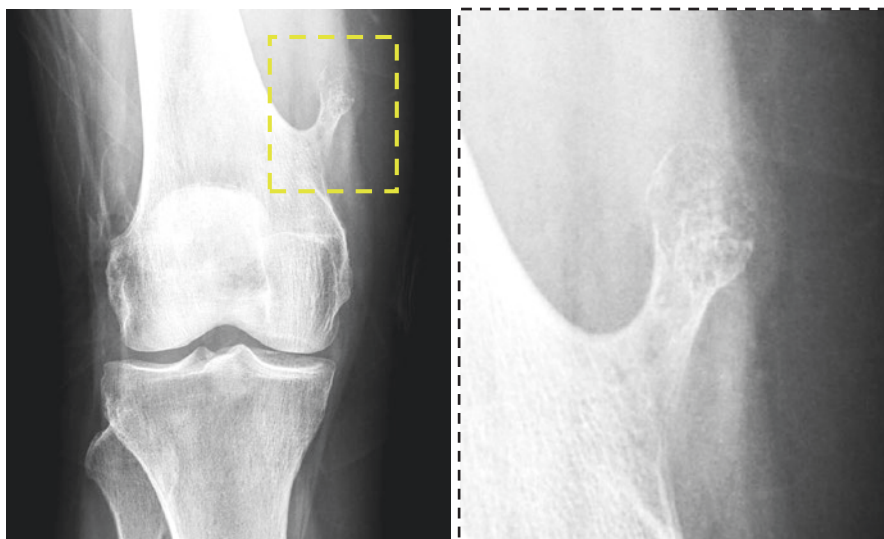


Fig. 15.39 Osteochondroma

Osteochondromas is a relatively common imaging finding. An osteochondroma is usually symptomless and most of the times is found incidentally. It is the most common benign bone tumour and usually occurs in the metaphyseal region of the long bones. Other commonly affected bones are the pelvic bones and the shoulder blades. Malignant transformation of a solitary osteochondroma may occur in 1–2% of patients, thus better imaging techniques should be used, particularly if there is a suspicion of malignancy, or even histological examination. In this figure, a typical pedunculated osteochondroma on the femur is shown (yellow rectangle). Note also the same lesion in magnification.



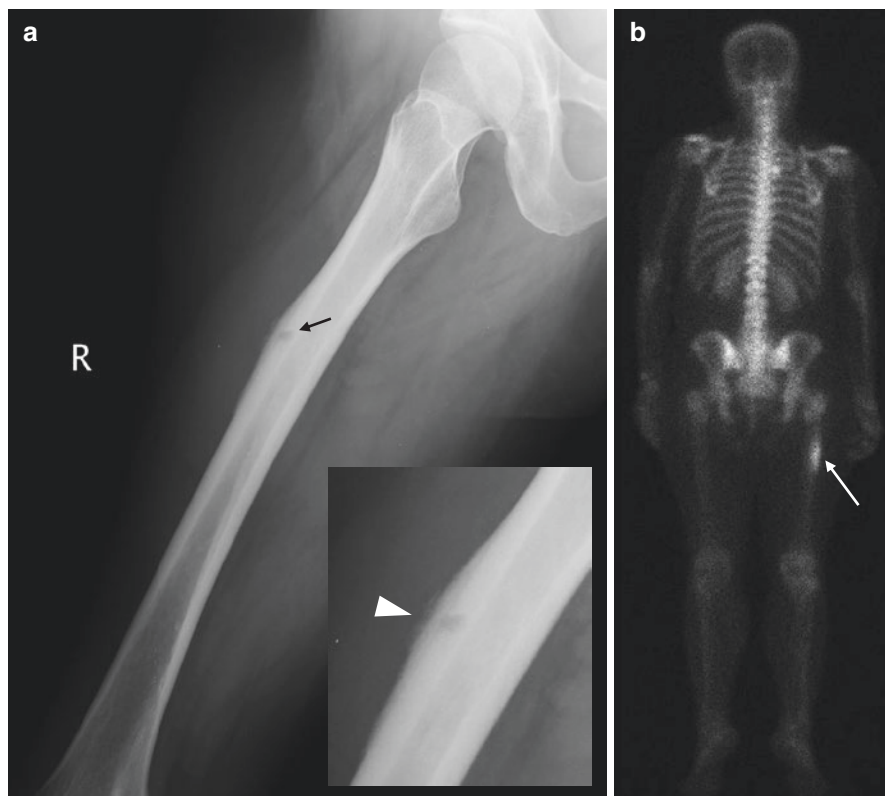


Fig. 15.41 Osteoid osteoma

Osteoid osteoma is a benign osteoblastic tumour. It was first described by Bergstrand in 1930. Osteoid osteomas are usually small (1.5–2 cm) characterised by an osteoid-rich nidus that is well demarcated and by a surrounding zone of sclerotic but otherwise normal bone. The condition appears in younger adults and it seems to have a predilection to the lower extremities which are the most common sites of appearance. This is a female patient (41 years old) that was complaining about a continuous, deep and aching pain of her right thigh that was worse at night. A plain radiograph (Fig. 15.41a) showed the appearance of an osteoid osteoma (proximal 1/3 of her right femur). A centrally located, oval radiolucent area (black arrow), surrounded by reactive sclerotic bone (inset figure in more detail – white arrowhead) is clearly seen. ^{99m}Tc -methylene diphosphonate bone scintigraphy image (Fig. 15.41b) revealed increased focal uptake (white arrow).

Fig. 15.40 Enchondroma

Enchondromas are classified under the term low grade chondral series tumours and are benign medullary cartilaginous neoplasms. They are relatively common and most of the times appear as an incidental finding on plain radiographs. Even when they are an incidental finding, other imaging modalities such as CT or MRI must be used in order to specify the exact extent of the lesion. Finally, a biopsy may be necessary to confirm the diagnosis. It may be difficult to distinguish these tumours from low-grade chondrosarcomas.

In Fig. 15.40a and b, a small enchondroma is seen at the 1/3 distal part of the femur (white arrowheads) whereas in Fig. 15.40c both 1st metatarsals are affected (white arrows). See also the insert figure of the 15.40c with the characteristic “ring and arc” appearance on CT (red arrow).

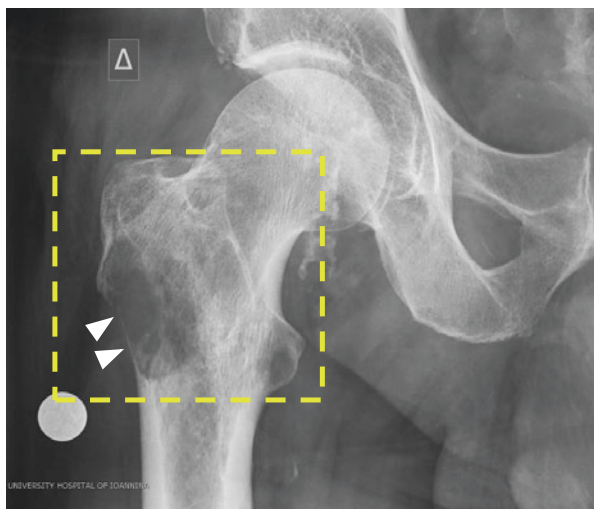


Fig. 15.42 Solitary or Unicameral bone cyst

A unicameral bone cyst, is considered to be benign since it does not spread beyond the bone. It can be found at the metaphysis of long bones. 50% of cases involve the proximal metaphysis of the humerus whereas 20% of cases involve the proximal femur (Fig. 15.42 – yellow rectangle – dashed lines). There is thinning of the cortical bone (white arrowheads) and depending on the size of the cyst, it can cause a pathological fracture.



Fig. 15.43 Multiple myeloma – raindrop skull

Multiple myeloma is the most common primary malignant bone neoplasm in adults. Numerous radiolucent lesions on the skull are seen in Fig. 15.43a (white arrows). This pattern of the lytic lesions is known as raindrop skull which is characteristic of multiple myeloma. The diagnosis was confirmed by bone marrow biopsy and aspirate samples that showed 50% clonal plasma cells in the marrow.

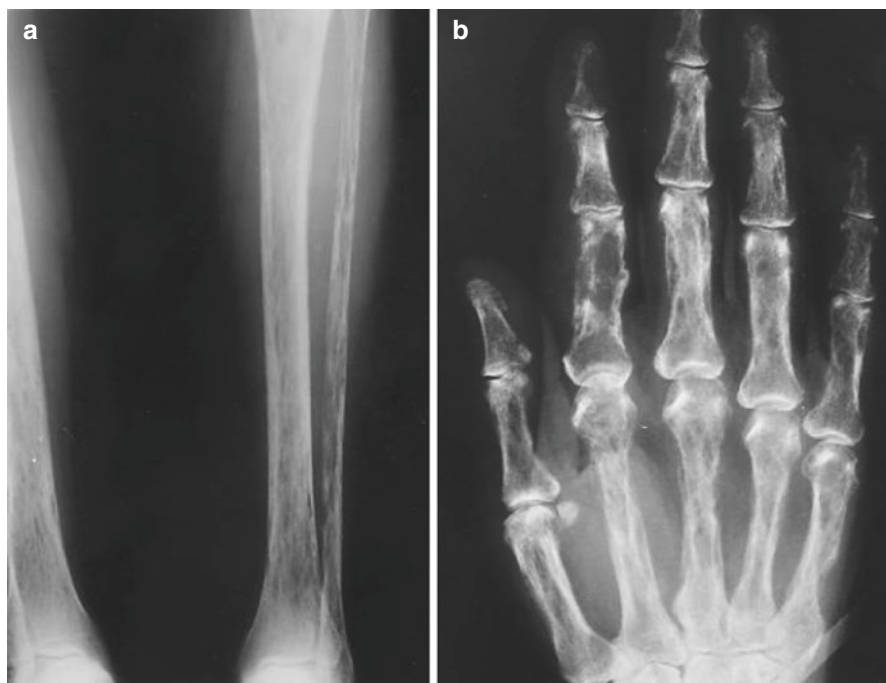


Fig. 15.44 T-cell lymphoma

Lytic lesions in a young lady with diffuse pain of the hands and lower extremities suffering from T-cell lymphoma grade IV. In Fig. 15.44a, the tibia and fibula are affected along the bone shafts whereas in Fig. 15.44b, the metacarpals as well as the digital bones are affected. You can notice the extensive lytic lesions affecting tibia and fibula as well as the phalanges of the hand.

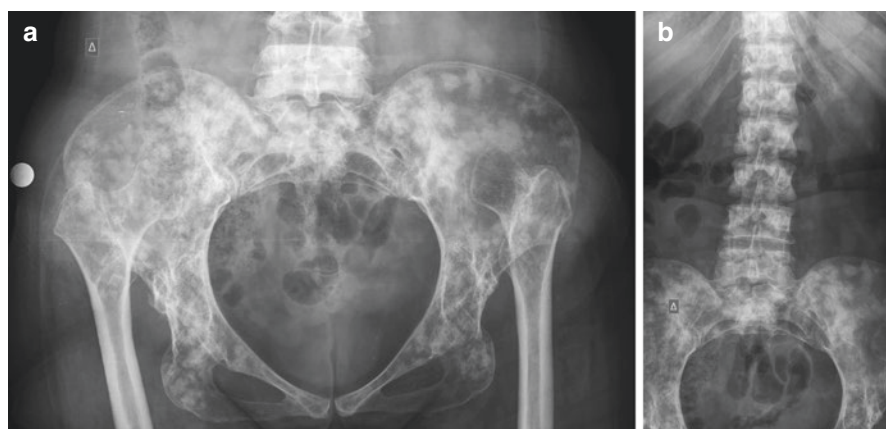


Fig. 15.45 Bone metastases

Lung cancer is the most common cause of cancer-related deaths worldwide. Bone is a common site of metastatic cancer spread in non-small cell lung cancer (NSCLC). Multiple bone metastatic lesions are much more common than single sites of bone metastases (80% and 20% respectively). The most common site of metastatic disease is the spine (45%). Pelvis may be affected in 20% of cases. This is a female patient, heavy smoker with lung cancer. As you can notice, there are multiple bone lesions of the pelvis (Fig. 15.45a) and spine (Fig. 15.45b). The patient was also suffering from bilateral congenital hip dislocation (Fig. 15.45a). Prognosis is poor in such patients

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Chapter 16

Adverse Drug Reactions in Rheumatology



16.1 Introduction

There is a high probability of developing adverse drug reactions (ADRs) in rheumatology. Corticosteroids (CS) as well as different classes of disease-modifying anti-rheumatic drugs (DMARDs) are the commonest suspected drugs for variable ADRs. Even if these drugs are widely known for their efficacy on rheumatic diseases, it is necessary to know what to expect and how to treat a possible ADR. At this chapter we present some common but also some more seldom ADRs.

16.2 Corticosteroids

CS are the first drugs used in Rheumatology. CS are used in most of the rheumatic diseases as adjunctive therapy for short-term administration (acute episode or exacerbation) or as maintenance therapy in selected cases (e.g. systemic lupus erythematosus - SLE, dermatomyositis - DM). CS may produce general ADR or from virtually any organ-system in the organism.

Gastrointestinal: nausea, vomiting, dyspepsia, diarrhea, hyperphagia, weight gain (truncal obesity and moon face), abdominal distension, pancreatitis, esophageal ulceration, silent intestinal perforation.

Skin: acne, hirsutism, impaired wound healing, thin fragile skin, petechiae, ecchymoses, facial erythema, increased sweating.

Blood: neutrophilia, lymphopenia, monocytopenia.

Ocular: posterior subcapsular cataracts, glaucoma.

Musculoskeletal: myopathy, avascular necrosis (especially of femoral and humeral heads), osteoporosis, stunt growth in children.

Cardiovascular: congestive heart failure, atherosclerosis, hyperlipidemia, hypertension.

Endocrinology: hypoadrenalism (if abruptly withdrawn), Cushing's syndrome, diabetes mellitus, menstrual irregularities.

Psychiatric: major depression, psychosis.

Serious infections have also been reported.

16.3 Cyclosporine

Cyclosporine (CSA) can cause nephrotoxicity, hepatotoxicity, fatigue, weakness, cramps, bloating, flushing, dyspepsia, nausea, abdominal pain, hypertrichosis, gingival hyperplasia, headache, tremor, paresthesias, arthropathy, muscle

cramps, hypomagnesemia, hyperuricemia, hyperkalemia, hyperglycemia, hyperlipidemia.

16.4 Methotrexate

Methotrexate (MTX) can cause general malaise, fatigue, fever, chills, dizziness, stomatitis, painful oral ulcers, nausea, pancytopenia, leukopenia, thrombocytopenia, megaloblastic anaemia, methotrexate-induced lung diseases, skin reactions, hepatotoxicity.

16.5 Hydroxychloroquine

Hydroxychloroquine (HCQ) may worsen psoriasis or porphyria and it can cause skin rashes, retinopathy with irreversible retinal damage, defects in accommodation with symptoms of blurred vision, halos around lights and photophobia, abnormal pigmentation of the retina, visual field defects, skeletal muscle palsies or skeletal muscle myopathy or neuromyopathy, anorexia, nausea, vomiting, dyspepsia, cramps, bloating, diarrhea, headaches, insomnia, nervousness, tinnitus, aplastic anaemia, leukopenia, agranulocytosis, thrombocytopenia.

16.6 Biologics

Biologic (b)DMARDs, including tumour necrosis factor (TNF) inhibitors, different molecules targeting interleukins and rituximab (targeting the CD20 molecules on B-cells) are generally safe options for various rheumatic diseases with the main adverse effect being predisposition to infections mainly of the upper respiratory system. Since the appearance of these molecules, there are several case reports reporting the ADRs after treatment with those agents. The reported adverse drug reactions could be simple allergic reactions at the site of injection (if injectable subcutaneously) to severe systemic allergic reactions (usually with the intravenous treatments). Many of these drugs can potentially cause autoimmune phenomena like positive anti-nuclear antibodies (ANA), and the formation of other autoantibodies as well as lupus like syndrome, myositis and autoimmune skin reactions like psoriasiform skin reactions, granuloma annulare (GA), vitiligo, pemphigoid etc. Herpes zoster (HZ) is also another adverse manifestation of these drugs.

Several cases of psoriasiform eruptions have been reported in patients suffering from rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other diseases treated with biological agents. The incidence of TNF- α inhibitor-induced psoriatic skin lesions has been estimated to be 3% in patients with spondyloarthropathies (SpA) and 4% in patients with RA. The mechanism underlying this paradoxical reaction has not been fully elucidated.

Although the prevalence of GA may be high among patients with chronic diseases, its occurrence in patients who receive TNF- α treatment exceeds the prevalence expected by chance. The exact cause of GA is unknown. Because of the histopathology and T-cell subtypes associated with the lesion, a delayed type of hypersensitivity reaction is suspected, but the initiating antigen has not been characterised. The underlying pathophysiological mechanism responsible for the development of GA after TNF- α remains unknown. It has been suggested that, under certain conditions, TNF inhibition promotes the activation of autoreactive T cells, leading to tissue damage by autoimmune mechanisms.

Vitiligo is a common skin disorder characterised by partial or complete loss of pigment-producing melanocytes within the epidermis. Most evidence supports autoimmune causation, focusing on the presence of circulating antibodies against melanocytes and the association of vitiligo with autoimmune disorders. TNF- α inhibitors have been reported to be the inducing agents for these skin lesions in many case reports.

In conclusion, the link between TNF- α inhibition and immune mediated skin lesion development in patients suffering from inflammatory arthropathies as well as various autoimmune diseases has been made.

16.7 Others

Any drug can potentially produce an ADR, but here we present only the ones in relation to the photos.

16.8 Corticosteroids



Fig. 16.1 Cushingoid facies

Cushingoid facies is the result of exogenous or iatrogenic Cushing syndrome in patients treated with CS for a long period of time. Patients develop a rounded appearance (moon facies) due to fat deposits on the sides of the face (Fig. 16.1a, b). Weight gain with fat redistribution such as moon facies is one of the most common signs of CS use. Nevertheless, moon facies does not always mean that it is the result of steroid intake. This is a reversible effect and dose-dependent. Usually, when steroid dose decreases, there is improvement of the signs too. To avoid steroid adverse effects, the lowest effective dose should be prescribed. In Fig. 16.1b you can also notice the extensive face telangiectasias (black arrows) as well as hypertrichosis around the mouth which are side-effects of prolonged treatment with CS. In Fig. 16.1c, the same patient as in Fig. 16.1a after minimizing the CS.



Fig. 16.2 Steroid-related skin atrophy

Steroid atrophy or CS-induced dermal atrophy could be the result of topical or systemic CS. In Rheumatology, systemic treatments are commonly used. Patients on long-term systemic CS usually present with notable skin atrophy on the upper and lower limbs. Topical CS are absorbed at different rates depending on the thickness of the stratum corneum and are also dependent of the form, potency and the content of other agents (e.g. keratolytic agents such as salicylic acid).

In Fig. 16.2, skin atrophy is significant with the characteristic “cigarette paper” appearance and increased visibility of the vessels. Non-palpable purpuric lesions (black thick arrows) and telangiectasias are common. Ecchymoses are found in up to one-third of rheumatologic patients treated with CS, instead of 2% without CS in their treatment. Newer ecchymoses have a more vivid red colour (black arrows), unlike the old ones, which get a brown colour due to haemosiderin deposition in the nearby tissue (yellow arrows). Finally, superficial ulcers (black circle) may appear which are difficult to treat and are prone to bacterial infections.



Fig. 16.3 Steroid acne folliculitis

CS acne folliculitis is a relatively common skin manifestation in patients who receive treatment with high-dose CS. With high-doses, an abrupt onset of CS acne after 1–2 weeks is observed. This drug-induced acne may appear as a side effect of short-term or long-term therapy. Usually, it appears commonly in early-adulthood, but it can appear at any age. Patients with a history of acne are particularly at risk. The distribution of CS acne folliculitis resembles that of severe acne vulgaris. The most common affected areas are the chest and back (as in the presented patient), face and shoulders.

The lesions are relatively uniform in shape and the colour is vivid-red at the beginning which later turns to a dull-red colour. At a later stage, dome-shaped papules appear (black arrows), sometimes topped by a soft abscess. Usually they do not scar but a slight scarring may remain after healing.

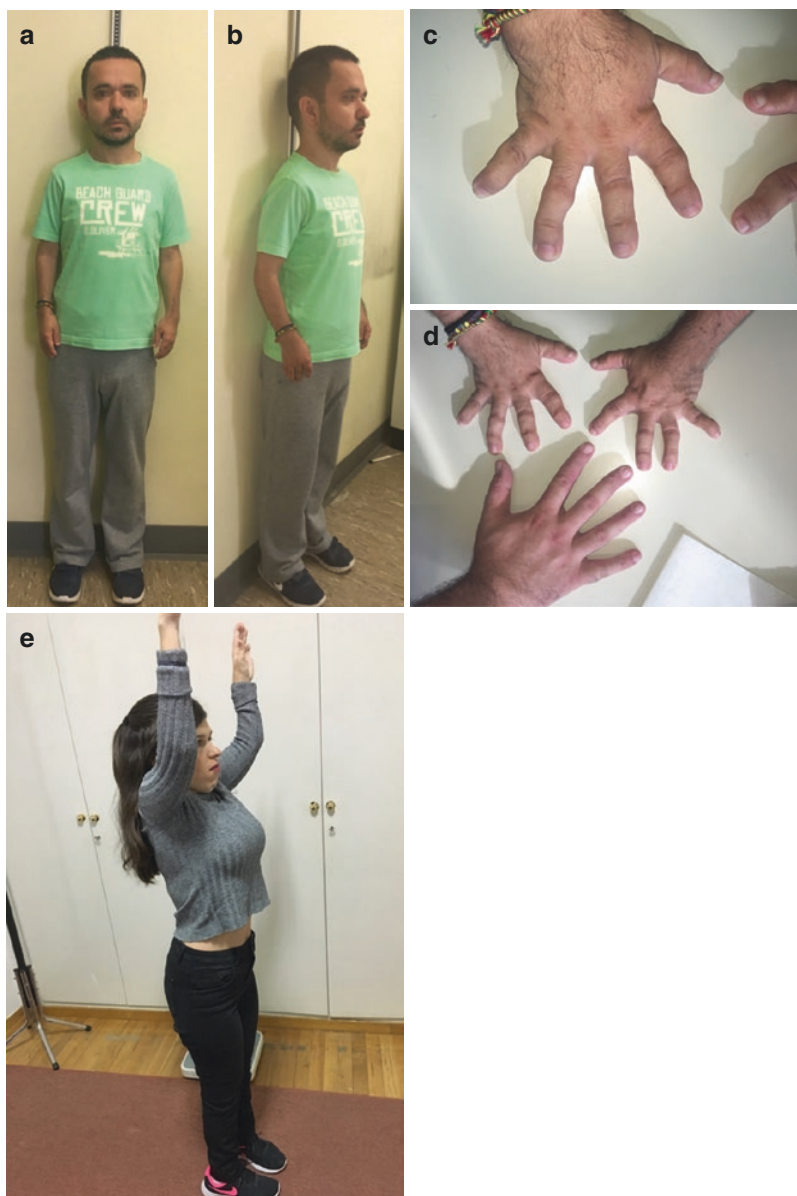


Fig. 16.4 Short stature

30-years old juvenile rheumatoid arthritis (JRA) patient with stunted growth due to steroids. His height is 148 cm (Fig. 16.4a, b). Depending on the type of JRA, non-steroidal anti-inflammatory drugs (NSAIDs), CS, conventional synthetic (cs)DMARDs as well as bDMARDs are used to reduce inflammation. CS should only be used sparingly because of their undesirable side effects at younger age in combination with the slower-than-normal growth observed in patients with JRA. In Fig. 16.4c patient's hand in more detail showing short digits, whereas in Fig. 16.4d patient's hand with a hand of a subject of the same age. Note the short digits of the patient in comparison with a healthy individual of the same age.

Figure 16.4e shows a 35-year old lady with short stature suffering from JRA.

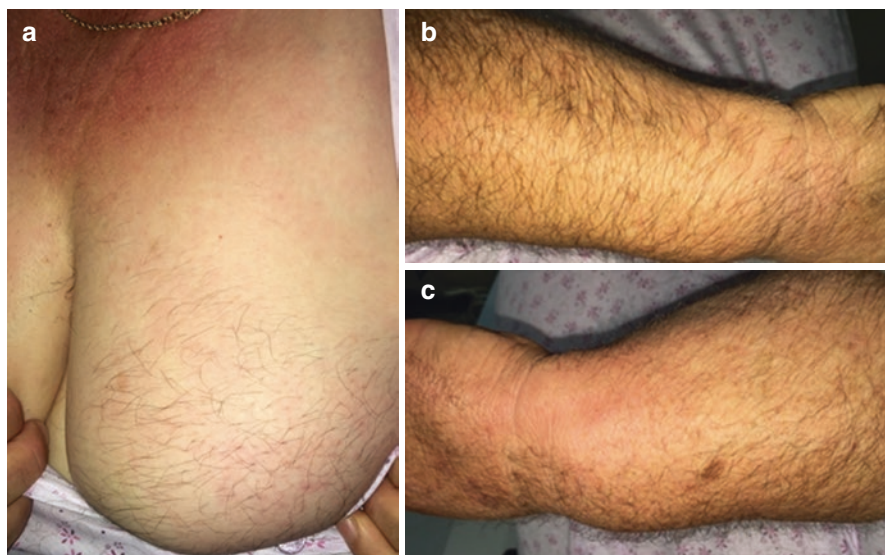


Fig. 16.5 Hirsutism

Hirsutism is called the hair growing in places where it normally does just for men (upper lip, chin, chest, abdomen, back of the trunk). It can be caused by hormones or medication. CS can cause this picture, as in this female patient with seronegative RA taking CS for a long period of time.



Fig. 16.6 Corticosteroid-induced avascular bone necrosis (aseptic bone necrosis)

CS use is one of the most important causes of avascular bone necrosis in rheumatology patients. The pathogenesis is not fully elucidated. Early recognition of this complication is of imperative importance as the prognosis is affected by the stage of the disease. Magnetic resonance imaging (MRI) is more sensitive than plain radiograph for diagnosing in early-stage. This is a plain radiography from a patient with established osteonecrosis of the right femoral head. You can notice the collapse of the femoral neck, extensive degenerative changes, joint-space narrowing and subchondral sclerosis.



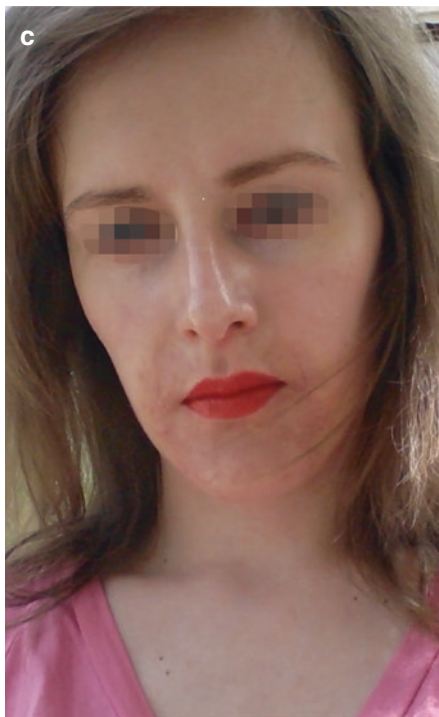
Fig. 16.7 Oral candidiasis

Oral candidiasis (oral thrush) is a not so uncommon manifestation in immunocompromised patients. Pseudomembranous and erythematous candidiasis are the most common forms. Some researchers consider pseudomembranous and erythematous candidiasis stages of the same entity, because of the fact that an erythematous surface is revealed beneath the pseudomembranes if wiped away. Sometimes there is minimal bleeding. Any part of the mouth can be affected but it usually appears on the tongue, buccal mucosae or palate. This is a 56-year old patient on a long-term CS use and the presence of oral candidiasis.



Fig. 16.8 Periorificial dermatitis

Periorificial dermatitis is a relatively common acneiform eruption of the face that is marked by erythematous papules. Sometimes scales may be present. Typically affects the perioral, perinasal, and periocular areas. This condition affects young adult women most commonly. Comedones are typically not present and enable its distinction from classic acne. Periorificial dermatitis may be induced by the use of cosmetic creams, make-ups and sunscreens but the most common aetiology in a rheumatology is the use of topical or oral steroids. Nasal steroids and steroid inhalers may also be the trigger. This is a patient suffering from SLE. After administration of oral CS, she developed the facial eruptions (perioral – black arrowheads and periocular – black arrows) as shown in Fig. 16.8a. Figure 16.8b and c show patient's eruption after treatment with 0.1% pimecrolimus cream for approximately 1 and 2 weeks respectively.

Fig. 16.8 (continued)**Fig. 16.9** Cyclosporine

CSA is a csDMARD with a well-known variety of side effects. In Fig. 16.9a, gingival hyperplasia or gingival hypertrophy is seen, whereas in Fig. 16.9b cherry hemangiomas or Campbell de Morgan spots affecting the abdomen. The latter appear typically in the elderly, but can be a side effect of CSA at younger ages, as in the patient presented here.



Fig. 16.9 (continued)

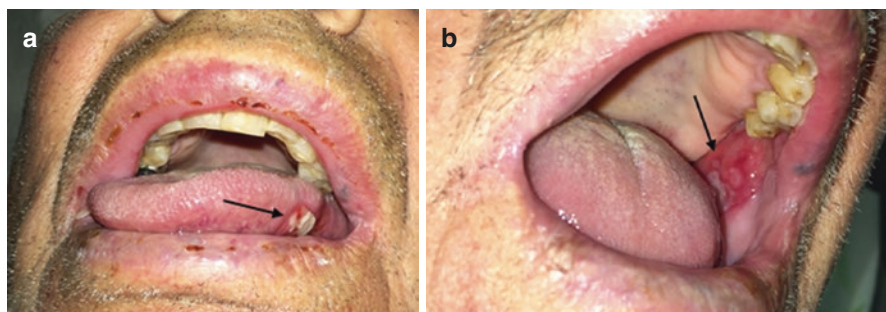


Fig. 16.10 Methotrexate

This 70-year-old patient presented to the Emergency Department with a burning sensation in his mouth after using 15 mg of MTX daily instead of using MTX weekly. On clinical examination he had also mouth ulcers and white patches in the oral cavity (black arrows) as well as on his lips. A full blood count (FBC) revealed pancytopenia. MTX overdose can be proved fatal (*see introduction for more details*). Another patient is shown in Fig. 16.10c. Marked erythematous, inflamed with small ulcerations soft palate is seen. Interestingly, the hard palate was covered by false denture and did not develop any lesions.



Fig. 16.10 (continued)



Fig. 16.11 Phototoxic reaction to hydroxychloroquine

In phototoxic reactions, the skin's appearance resembles sunburn, and the process has a fast onset. The skin rash is mainly confined to the sun-exposed areas and the reaction typically clears up after the drug is discontinued. Note the sharp demarcation between the sun and non-sun exposed skin in a patient with short suit (black arrows) treated with HCQ.

Fig. 16.12

Hyperpigmentation after
phototoxic reaction to
hydroxychloroquine

As described in Fig. 16.11, phototoxic reactions take place to the sun-exposed areas. HCQ is not an uncommon precipitating factor. The drug may become activated by exposure to sunlight and cause damage to the skin. Ultraviolet A (UVA) radiation is most commonly associated with phototoxicity, but ultraviolet B (UVB) and visible light may also contribute to this reaction. Hyperpigmentation of the affected area of the skin may develop after the resolution of a phototoxicity reaction. High doses of the drug and long exposures to sunlight may be required to cause the reaction. This patient was using HCQ for mild arthralgias due to RA and was spending many hours under the sun while gardening. Note the extensive hyperpigmentation affecting the face as well as the upper part of the chest.

**Fig. 16.13** Hydroxychloroquine-induced erythroderma

The term erythroderma (also called exfoliative dermatitis) consists of diffuse erythema and scaling of the skin. A variety of cutaneous and systemic conditions can cause erythroderma but the most common cause is an exacerbation of preexisting dermatoses. In the case of drug-induced erythroderma, onset may be abrupt with skin eruptions which coalesce and occupy large skin areas. HCQ, has mild immunomodulatory, anti-inflammatory, and photoprotective effects with a good safety profile. HCQ has rarely been reported as a cause of erythroderma. The exact pathogenesis is not known. Symptomatic treatment is given with emollients, low to mid-potency CS and oral antihistamines.

In Fig. 16.13a and b, the initial phase is depicted with the presence of diffuse erythematous lesions of the skin over hands and feet, whereas in Fig. 16.13c and d, exfoliation of skin over the hands and feet. The lesions settled with no scarring left. The histologic findings were hyperplastic stratified squamous epithelium with mild spongiosis and perivascular moderate lymphocytic infiltrate of the dermis.





Fig. 16.14 Skin discoloration after long-term treatment with hydroxychloroquine

Antimalarials such as HCQ are generally well tolerated when compared with other csDMARDs. On the other hand, pigment changes of the skin are not uncommon as described in the previous figures. Hyperpigmentation of the skin is one of the most common skin manifestations in patients treated with HCQ in long-term. The skin discoloration may be found in different skin areas. Figure 16.14a–d illustrate some examples of patients with skin hyperpigmentation of the upper back, axillae and legs. The site of predilection is the pretibial region of the lower limbs. When the skin discoloration affects flexor surfaces such as the axillae (ie patient in Fig. 16.14b) it is difficult to differentiate between acanthosis nigricans and skin discoloration due to HCQ. A histologic evaluation is an imperative, as acanthosis nigricans could be a paraneoplastic phenomenon.

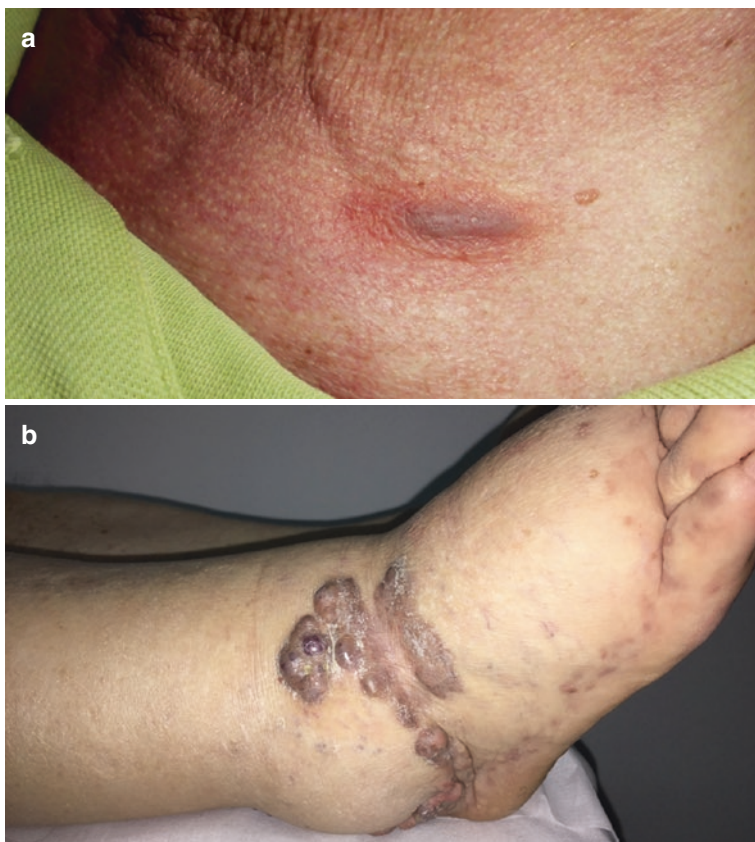


Fig. 16.15 Kaposi's sarcoma

Kaposi's sarcoma is a lymphoangioproliferative neoplasm induced by human herpes virus 8 but iatrogenic immunosuppression is another well-established variant. It is a rare condition among patients receiving immunosuppression for different autoimmune disorders. Figure 16.15a shows a patient with Kaposi's sarcoma on the lateral side of the neck. He was diagnosed with granulomatosis with polyangiitis (GPA) and was treated with cyclophosphamide (CP) and CS. Figure 16.15b shows a more extensive lesion of a woman in immunosuppression.

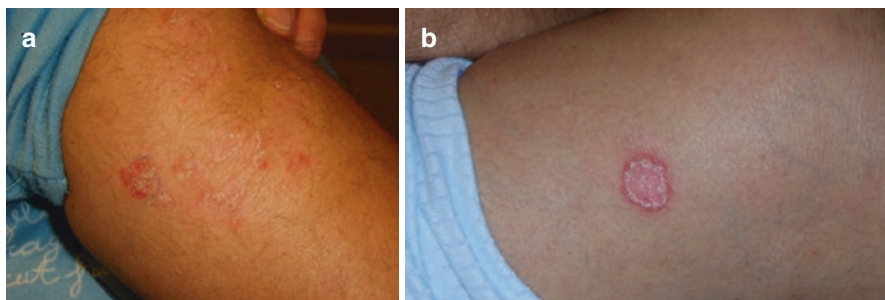


Fig. 16.16 Skin lesions after administration of rituximab

Rituximab is a chimeric monoclonal therapeutic antibody which causes depletion of CD20-positive B cells. Apart from its apparent efficacy in the treatment of non-Hodgkin lymphoma and of several rheumatic diseases, it is associated with ADRs including the induction of autoimmune phenomena such as this in Fig. 16.16a and b. An RA patient developed psoriatic skin lesions after the second course of treatment with rituximab. The psoriatic skin lesions were confirmed histologically. The term “de novo” psoriasis is currently used to describe this kind of lesions.

Fig. 16.17 Allergic

reactions to TNF-inhibitors
In general, TNF-inhibitors have a good safety profile. Their efficacy is well-recognised in everyday clinical practice. However, a small proportion of patients may develop adverse skin reactions. These reactions can be limited to the site of the injection (if the administration is subcutaneous) developing a mild erythema, or can be systemic. The patient in Fig. 16.17 developed facial flushing with lip oedema (Fig. 16.17a) and a tingling sensation in her mouth with a generalised skin rash (Fig. 16.17b) and intense pruritus during the first infusion with infliximab. Systemic allergic reactions should be treated adequately because they may be proved fatal. Always check for a patent airway.





Fig. 16.18 Pemphigoid after administration of TNF-inhibitors

Bullous pemphigoid (BP) is an uncommon skin condition in which erythematous, urticarial papules and plaques progress to form tense bullae, typically in elderly men and women. It is well described in bibliography that TNF-inhibitors can develop this condition. This is a 58-year old lady suffering from RA treated with adalimumab. In Fig. 16.18a, both arms are involved. Figure 16.18b shows the characteristic blisters which contain clear fluid and are newly formed. In Fig. 16.18c, old (red arrow) and new (black arrow) lesions can be seen. If ruptured, blisters may become infected, so a good local hygiene is needed.



Fig. 16.19 Granuloma annulare after administration of TNF-inhibitors

GA consists of smooth discoloured plaques. They are usually thickened and ring-shaped or annular in shape. A 49-year old woman with long-standing seropositive RA was treated with infliximab (3 mg/kg) every 8 weeks. She was refractory to MTX and CS and responded well to infliximab therapy. Nine months after the initiation of treatment, she developed localised GA lesions (Fig. 16.19a), which was confirmed by skin biopsy. Infliximab was discontinued and local corticosteroids were used. The resolution of the eruptions came 3 weeks later. Another case is depicted in Fig. 16.19b and c with a generalised form of GA in an RA patient treated with adalimumab. GA is a delayed hypersensitivity reaction to some component of the dermis. Inflammation is mediated by TNF- α but the exact reason why this occurs is unknown.



Fig. 16.20 Herpes zoster infection

HZ infection is more prevalent in immunocompromised patients in contrast to the general population. It is characterised by a painful blistering rash in a specific area of skin (dermatome). The lesions appear as a crop of red papules which tend to spread. The blisters may become pustules and then they form crusts. The herpetic lesions, usually spread in a unilateral distribution but may be bilateral. Post-herpetic neuralgia is the most common complication and it is a continuous burning sensation with increased sensitivity in the affected areas or a spasmodic shooting pain. In the above figures, two patients treated with different TNF inhibitors developed herpes zoster infection. Figure 16.20a and b depict a more severe lesion with blisters and crusts whereas in Fig. 16.20c and d the crops of red papules are evident.



Fig. 16.21 Herpes zoster – unusual presentation

This is a zosteriform radicular pattern of skin eruption corresponding to dermatomes C6, C7, and C8 in a patient with RA treated with a bDMARD against the interleukin-6 receptor. The distribution of this HZ infection is uncommon. The black arrows in Fig. 16.21a show the distribution of the skin eruptions, whereas the eruption within the yellow dashed rectangle are shown in detail in Fig. 16.21b.

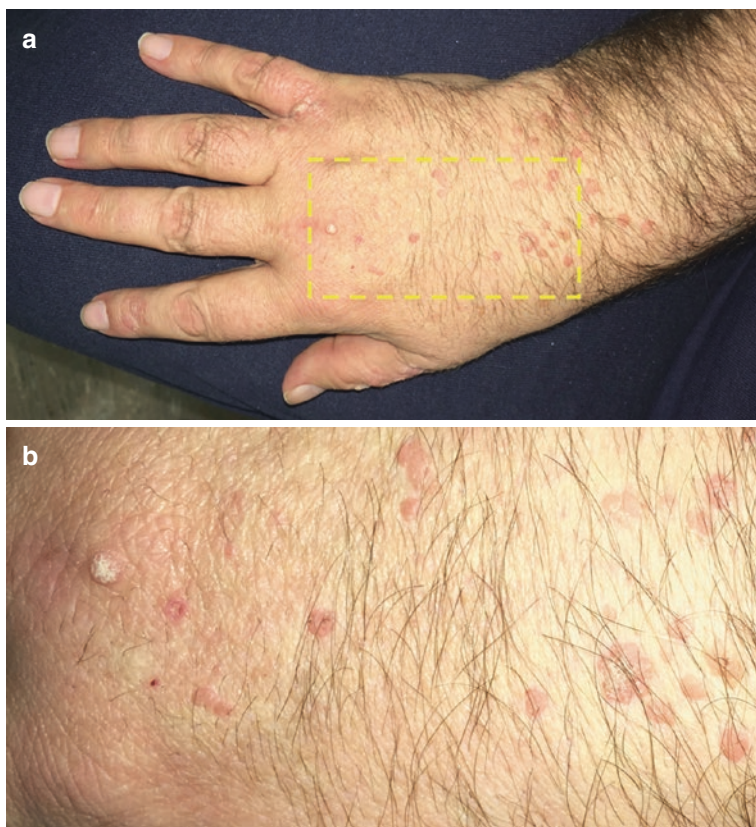


Fig. 16.22 Infliximab-associated psoriasiform dermatitis

TNF-inhibitors, such as infliximab, are effective agents in the treatment of various inflammatory/autoimmune disorders. Anti-TNF- α induced psoriasiform dermatitis is an infrequent complication but it has been well-described in bibliography. This is an RA patient treated with infliximab for several years that developed erythematous, scaly skin lesions on the extensor surfaces of both upper limbs (Fig. 16.22a). Biopsy revealed psoriasiform dermatitis, consistent with a diagnosis of anti-TNF- α induced psoriasiform dermatitis. After discontinuation of Infliximab and use of topical steroid agents (clobetasol), there was complete resolution of the skin lesions. Figure 16.22b shows the skin lesions in more detail.



Fig. 16.23 Subconjunctival haemorrhage

Long-term use of NSAIDs can cause subconjunctival haemorrhage as in this patient treated for seronegative arthritis.

It is generally a benign, self-limiting condition that requires no treatment. Sometimes, it can be confused with episcleritis especially in patients suffering from a seronegative spondyloarthropathy.

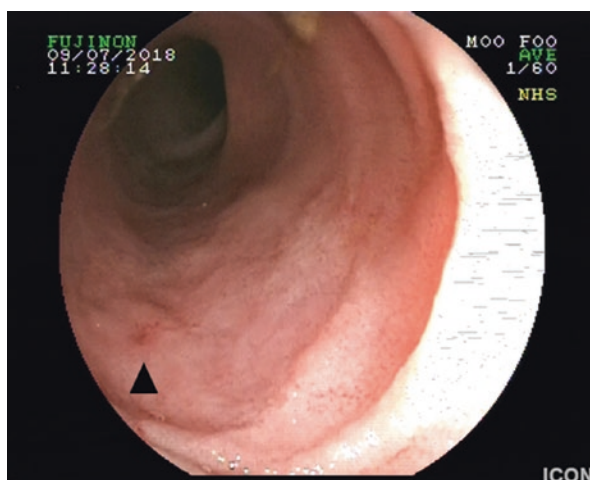


Fig. 16.24 Intestinal ulcer

Gastrointestinal ulcers are a common feature of long-term use of NSAIDs. Gastric and duodenal ulcers are the commonest. Until recently, gastrointestinal injury by NSAIDs was studied mainly in the upper gastrointestinal tract, but there is a growing evidence that there is NSAID-related damage in the distal small bowel and colon, most commonly in the ileocecal region. This is an RA patient with an ulcer at the terminal ileum (black arrowhead) using diclofenac 75 mg for >2 weeks.

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